

ASTHMA AT NIGHT

Observations on the interrelations of  
asthma and sleep

J R CATTERALL

BSc (1972), MB, ChB (1975), MRCP (UK)

A dissertation submitted to the University of Edinburgh  
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Department of Respiratory Medicine  
University of Edinburgh  
Scotland

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### ERRATA

Fig 16a      The lower limit of the scale for  
               $T_e$  is 1.5 sec, not 0.5 sec.

Figs 16b      The coefficient of variation is  
and 17        standard deviation/mean, not  
              mean/standard deviation

## INTRODUCTION

Patients with asthma often have symptoms at night (Floyer, 1698; Turner-Warwick, 1984), with maximal bronchoconstriction in the early hours of the morning (Turner-Warwick, 1977). There is also evidence for an excess of nocturnal deaths due to asthma (Cochrane and Clark, 1975; Lancet, 1983). However, the causes and physiological consequences of nocturnal bronchoconstriction in asthma are poorly understood (Turner-Warwick, 1977; Barnes, 1984; Douglas, 1985).

Recent studies have emphasised that sleep itself can cause changes in respiration. Perhaps the best known example of this is the sleep apnoea syndrome (Guilleminault et al, 1976, 1978), in which intermittent cessation of breathing during sleep causes loud snoring at night and hypersomnolence during the day, symptoms that often lead to marriage problems and difficulties with employment and driving. In infants, sleep apnoea may have even more tragic consequences, for it has been implicated in some cases of the sudden infant death syndrome (Steinschneider, 1972; Guilleminault et al, 1986). In chronic bronchitis and emphysema, marked falls in arterial oxygen saturation occur during sleep in the absence of apnoea (Flick and Block, 1977; Douglas et al, 1979b; Catterall et al, 1983). These nocturnal hypoxaemic episodes in chronic bronchitis and emphysema

also may be important clinically, for there is evidence that they contribute to the development of pulmonary hypertension (Douglas et al, 1979a; Boysen et al, 1979; Fletcher and Levin, 1984; Catterall et al, 1985), cor pulmonale (Moore-Gillon and Cameron, 1985) and secondary polycythaemia (Moore-Gillon and Cameron, 1985).

In 1978, I began research into the mechanism of transient nocturnal hypoxaemia in chronic bronchitis and emphysema. This work, which was initiated by Professor D C Flenley and Dr N J Douglas in the Department of Medicine, University of Edinburgh is reported in detail elsewhere (Catterall et al, 1983a,b and 1985; Brezinova et al, 1982; Calverley et al, 1982). In the course of these investigations, however, I became aware that there had been no similar studies in asthmatic patients, despite the fact that they have more nocturnal symptoms than patients with chronic bronchitis and emphysema. I wondered whether asthmatic patients might become hypoxaemic during sleep and also whether sleep itself might be a cause of nocturnal bronchoconstriction in asthmatic patients.

I therefore began to investigate the relationships between sleep and breathing in patients with asthma. These investigations are the subject of my thesis.

Part I of the thesis contains a brief review of the clinical importance of nocturnal asthma, and an account of the methods used to study breathing during sleep.

The original work of the thesis is divided into three further parts: In Part II are described studies of breathing and oxygenation during sleep in normal subjects. These studies were performed to establish a normal range of apnoea, hypopnoea and oxygenation during sleep and to determine the effects of age and sex on these variables.

Part III contains the results of similar studies in patients with asthma. Breathing patterns and oxygenation during sleep in asthmatic patients were compared with those of normal subjects and those of patients with chronic bronchitis and emphysema.

The studies described in Part IV were designed to explore the relationship between sleep and bronchoconstriction. I wished to establish whether sleep was essential for nocturnal bronchoconstriction and to determine whether bronchoconstriction was associated with one particular stage of sleep.

The results are summarised at the end of each section, and the clinical implications of the results are discussed in Part V.

## Part I

### BACKGROUND AND METHODS

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## Chapter 1

### **THE CLINICAL IMPORTANCE OF NOCTURNAL ASTHMA**

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The term asthma is derived from the greek word meaning "laboured breathing" (Onions, 1966). In the early history of the disease, the word "asthma" referred to a symptom, and confusion with other causes of breathlessness occurred (Major, 1953). Nocturnal "asthma" appeared very early in the literature, but in view of the frequently loose use of the word, it is difficult to be certain when the nocturnal occurrence of bronchial asthma was first reported (Hetzl, 1980).

#### **1. The recognition of nocturnal asthma**

One of the earliest convincing descriptions of nocturnal asthma was by Aurelianus Caelius in the 4th or 5th century AD (De morbis acutis and chronicis, 1709). The first physician to associate asthma with bronchoconstriction, however, was Willis (1649) some 1300 years later. Both of these physicians were familiar with the tendency for asthmatic attacks to occur at night, but perhaps the most vivid and complete descriptions of nocturnal asthma were made by Doctor (later Sir) John Floyer (1698), himself an asthmatic. Cullen (1784), Bree

(1797), Reisseissen (1822), Laennec (1827) and Trousseau (1868) also described nocturnal asthma. Salter (1868), who introduced the concept of bronchial hyperreactivity, commented that nocturnal attacks were the most constant feature of the disease. He also observed that airways obstruction could be present during sleep, reporting a case whose wheezing did not immediately waken the patient, but could, nevertheless, be heard in the next room. Thorowgood (1878) considered nocturnal asthmatic attacks to be more frequent "towards early morning" and he discussed treatments for nocturnal asthma which included the anticholinergic agents, stramonium and belladonna.

## **2. The measurement of nocturnal bronchoconstriction**

Although these physicians were aware of nocturnal asthma, they were not able to measure the extent to which airflow limitation increases at night. In 1960, Lewinsohn and colleagues measured forced expiratory volume in 1 second ( $FEV_1$ ) at intervals during the day in 5 healthy subjects and 12 patients with "generalised airway obstruction", including some with asthma.  $FEV_1$  fell in the early morning in both groups, but this fall was much greater in the patients with airway disease than in the healthy subjects. Further studies (McDermott, 1966; Guberan et al, 1969; Reindl et al, 1970; Reinberg et al, 1970; Kerr, 1973) confirmed that there is a normal circadian variation in airways resistance, the highest resistances and the lowest peak expiratory flow rates occurring during the night, and that this is greatly magnified in patients with asthma (Reinberg et al, 1970; Reindl et al, 1970; Turner Warwick, 1977; Connolly,



1977; Hetzel and Clark, 1980) but not in patients with chronic bronchitis and emphysema (Zedda and Sartorelli, 1971; Connolly, 1979; Dawkins and Muers, 1981). Turner-Warwick (1977) coined the term "morning dips" for these early morning falls in peak expiratory flow rate (PEFR) in asthma.

In a study of 16 asthmatic patients with morning dips in PEFR, Hetzel and colleagues (1977b) showed that the percentage rise in PEFR between 6 am and 2 pm was similar to the percentage changes in  $FEV_1$  and specific conductance, and that these changes were accompanied by hyperinflation and gas trapping. Thus, their results confirmed that there are large circadian variations in airflow limitation in asthma and that PEFR is a reliable index of the severity of nocturnal and early morning asthma.

In the same study, Hetzel and colleagues (1977b) attempted to determine the probable site of airways obstruction in early morning asthma. Specific airways conductance increased more than twofold between 6 am and 2 pm, suggesting that there was a considerable increase in obstruction of the large airways during the night (Cotes, 1975). To determine the relative importance of large airway narrowing and small airway narrowing, they also studied diurnal changes in the response of the maximal expiratory flow rate to a helium-oxygen mixture. Two patients showed a response to helium (Despas et al, 1972) at all times, seven were consistent non-responders, and seven had a variable response. These results were unhelpful in determining the relative contributions of large and

small airways to circadian changes in airflow limitation, possibly because the low flow rates generated by some of their patients may have rendered the test invalid (Hetzel, 1984). Mak and colleagues (1982) reconsidered this question, studying eight asthmatic children with less severe airflow limitation than in the adult study. Response to oxy-helium mixture was similar at both of the times studied (8 am - 9 am and 5 pm - 6 pm), and this was interpreted by the authors as evidence that both large and small airways are involved in the circadian variation of pulmonary function in asthma. However, these children had relatively mild asthma and the mean circadian variation in PEFr recorded during the study, although statistically significant, was only 5%.

In conclusion, there is evidence that large airway narrowing occurs in nocturnal asthma but the importance of small airway narrowing is unclear. The severity of nocturnal and early morning asthma can be assessed by measurements of PEFr.

### **3. The prevalence of nocturnal bronchoconstriction in asthma**

Hetzel and Clark (1980) used cosinor analysis to compare normal and asthmatic circadian rhythms in peak expiratory flow rate (PEFR). They made PEFr measurements four times daily in 221 normal individuals of whom 145 (66%) showed a significant circadian rhythm in peak expiratory flow rate, and 56 asthmatic patients, of whom all showed significant circadian variation of PEFr on cosinor analysis. The amplitude of the PEFr rhythm in the asthmatic patients (mean 51% of each individual's average daily PEFr) was significantly greater

than that in the 145 normal subjects with PEFr rhythms (mean 8.3%), but the mean phases of the normal and asthmatic rhythms were not significantly different, the highest daily PEFr occurring between 2 pm and 10 pm in the great majority of subjects in each group. The authors concluded that nocturnal bronchoconstriction in asthma probably represents an exaggeration of a normal circadian rhythm and they suggested that a diurnal PEFr rhythm amplitude exceeding 20% of the mean daily PEFr might be a useful screening test for asthma. However, not all patients with asthma have "morning dips" (Turner Warwick, 1977). Connolly (1979) recorded peak flow rates five times daily for at least four days in 115 asthmatics, and found that about one-third regularly bronchoconstricted overnight, a further third bronchoconstricted before sleep and remained bronchoconstricted overnight, whilst another third showed no circadian pattern. Furthermore, the observations in both these studies (Hetzel and Clark, 1980; Connolly, 1979) were based on asthmatic patients in hospital or immediately after discharge, and less marked circadian fluctuations in PEFr may be seen in asthmatic out-patients or patients in remission. Johnstone and colleagues (1984), for example, using cosinor analysis on measurements made three times daily, found that the mean circadian variation in PEFr in 63 asthmatic schoolchildren was 12% of the average daily peak flow, and Ryan and colleagues (1982) observed a mean circadian PEFr variation (based on two measurements daily and expressed as a percentage of the maximum daily value) of only 7.5% in 27 adult asthmatic out-patients. At present, therefore, although nocturnal bronchoconstriction is common in asthma, it is not possible to define a threshold for

circadian variation in PEF by which asthma can be diagnosed.

Nevertheless, interval measurements of peak expiratory flow over the 24 hour period are of great value in the clinical assessment of asthmatic patients (Turner-Warwick, 1977; Hetzel et al, 1977a, b; Bateman and Clark, 1979). They have also facilitated the study of nocturnal asthma, including the investigation of its causes (see Part IV) and the assessment of its clinical significance.

#### **4. The clinical consequences of nocturnal asthma**

**Morbidity:** Nocturnal symptoms are common in asthma. In a study of patients attending asthma clinics at two centres in the UK, some two-thirds of patients stated that they had nocturnal attacks of asthma and/or chest tightness on waking in the morning (Turner-Warwick, 1984).

**Mortality:** Fortunately, mortality from asthma is much less common than morbidity. Nevertheless, in England, Scotland and Wales some 1500 deaths per year are attributed to asthma, and approximately one-tenth of these are in patients aged 5 - 34 years (Office of Population, Censuses and Surveys, England and Wales, 1974-1984; Annual Report of the Registrar General for Scotland, 1974-1984). Although asthma in the old and very young may be confused with other conditions that cause wheeze and dyspnoea (Speizer et al, 1968a), the asthma fatality figures compiled for other age groups, especially the 5 - 34 year group (Speizer et al, 1968a; Jackson et al, 1982), are accurate. Furthermore, there have been well documented epidemics of

asthma mortality in recent years - one in the 1960's affecting Britain, New Zealand, Australia and Ireland (Fraser and Doll, 1971) and another current epidemic affecting the population of New Zealand (Jackson et al, 1982). Recent figures indicate that the death rate from asthma is also increasing again in England and Wales (McBurney, 1986). These figures emphasise the potentially serious nature of asthma.

The relationship between asthma deaths and nocturnal bronchoconstriction has been studied by a number of authors. Hetzel and colleagues (1977a) analysed 10 sudden deaths and ventilatory arrests in 1169 consecutive hospital admissions for asthma. The risk of sudden death or ventilatory arrest could not be related to the severity of the attack of asthma but it did correlate with the presence of marked diurnal variation in the peak expiratory flow rate. Two deaths after a sudden attack of asthma in young people were reported by Bateman and Clarke (1979) from a clinic set up to identify and manage such "at risk" patients. Both these patients had been shown to have marked diurnal variation in PEFr. These authors concluded that a wide diurnal variation in PEFr may be a better guide to recognition of the susceptible patient than "other factors such as length of history, age of onset, allergic factors, etc."

Although these observations demonstrate that a wide circadian variation in PEFr is associated with an increased risk of dying from asthma at any time of day, they do not prove that the nocturnal

asthmatic attacks are the immediate cause of death. Cochrane and Clark (1975) analysed asthma deaths occurring in 1971 in the Greater London hospitals in the 35-64 year old age group. They observed that 13 of the 19 deaths attributable to asthma occurred between midnight and 8 am. This initial study was followed by two studies from Cardiff in which asthma deaths in all age groups, both in and out of hospital, were analysed. In the first (Macdonald et al, 1976a), 90 deaths due to asthma were reported and death was noted to be more common in patients who had recently been discharged from hospital after a previous attack. The time of death was known in 79 of the 90 patients and showed no significant trend, but actual details of the times were not given nor was the method of analysis stated. The second paper (Macdonald et al, 1976b) reported 53 deaths over the same period of time (1963-74) that occurred in hospital. The hour of death was known in 44 of the 53 subjects and again showed no significant trend. Twelve patients were given assisted ventilation and therefore the time of nocturnal death may have been obscured as no data was given of the time that assisted ventilation was initiated. Hetzel et al (1977a), however, in their analysis of sudden deaths and ventilatory arrests due to asthma, observed that 8 of 10 ventilatory arrests occurred between midnight and 8 am.

Data on time of death from the four largest reported studies on asthma mortality (Cochrane and Clark, 1975; Macdonald et al, 1976a and b; British Thoracic Association, 1982), including previously unpublished data, was recently combined, and analysed together

(Lancet, 1983). Of the 219 deaths for which time of death was known, 93 had occurred between midnight and 8 am, indicating a significant ( $p < 0.01$  on chi square) excess of nocturnal deaths. The increase in death rate between midnight and 8 am in these asthmatics was 28%, much higher than the average 5% increase in death rate at night in the general population (Smolensky et al, 1972).

At best, therefore, nocturnal asthma is a nuisance, a minor symptom to which the patient can become accustomed (Hetzel et al, 1977b). At worst, it can threaten life and even occasionally kill.

Despite the clinical importance of nocturnal bronchoconstriction in asthma, its causes and physiological consequences are poorly understood. The purpose of the studies in Part III of this thesis was to investigate the effects of asthma on electroencephalographic sleep patterns, and to study nocturnal oxygenation and breathing patterns in asthmatic patients. Before this could be done, however, it was necessary to establish a normal reference range for irregular breathing and oxygenation during sleep; this was the main purpose of the studies in part II of the thesis. The studies in Part IV were designed to examine the relationship between sleep and airway calibre.

## Chapter 2

### **METHODS AND EVALUATION OF EQUIPMENT**

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Ideally, the methods used to study the physiology and pathophysiology of sleep should satisfy at least four criteria:

- (i) They should permit the investigator to define when the patient is asleep.
- (ii) The methods used should interfere with sleep as little as possible.
- (iii) They should be suitable for continuous recording, since sleep is now known to comprise a number of different stages (Aserinsky and Kleitman, 1953).
- (iv) They should also be performed at night since that is when sleep is most likely to be normal (Dahlgreen, 1981).

In addition, if studies are to be used clinically, it is important that the methods and equipment be acceptable to patients.

The first study of breathing and oxygenation during sleep to satisfy all of these criteria was described by Aserinsky in 1965. This study combined three techniques which previously had been described



separately: the definition of sleep and different sleep stages by electroencephalography, electromyography and electrooculography; the non-invasive measurement of arterial oxygen saturation by ear oximetry; and the monitoring of breathing patterns by methods which do not involve physical connection to the airway.

These were the methods used in the studies described in parts II and III of the thesis. In part IV I studied the relationship between sleep and airway calibre. This chapter contains a review of the development and principles of these methods.

#### **1. Definition of sleep and different sleep stages**

In early studies of the relationship between sleep and respiration (Smith, 1860; Mosso, 1878; Loewy, 1890; Magnus-Levy, 1894; Gujer, 1928; Ostergaard, 1944; Doust and Schneider, 1952; Robin et al, 1958), sleep was defined by behavioural criteria - either by observation alone or by the failure of the subject to respond to external stimuli. However, these criteria are highly subjective and there must be some doubt as to whether the subjects were always asleep when measurements were made. In most of the studies, moreover, sleep was assumed to be a homogeneous state.

The modern era of research into the physiology of sleep began in 1953, when Aserinsky and Kleitman first described rapid eye movement sleep (REM sleep), and its association with a characteristic electroencephalographic pattern, dreaming, and changes in autonomic nervous system activity including respiration. This important

discovery demonstrated conclusively that the traditional view of sleep as a homogeneous state was incorrect, and indicated that pre-existing observations or theories regarding sleep had to be re-examined or re-interpreted taking the stage of sleep into consideration.

In this thesis, sleep is staged using the criteria of Rechtschaffen and Kales (1968) who divide sleep into rapid eye movement (REM) and subdivisions of non-rapid eye movement (NREM) sleep, according to electroencephalographic (EEG), electromyographic (EMG) and electrooculographic (EOG) features which are outlined briefly in table 1.

These criteria are now widely accepted and allow reasonable comparisons between studies. Sleep is a cyclical process, which always starts in normal subjects with NREM sleep. Periods of REM sleep are interspersed throughout NREM sleep and occur approximately every 90 minutes throughout the night, lasting approximately 15 minutes in the first REM period, the subsequent REM periods tending to be progressively longer (Williams et al 1974). It is thus possible to predict roughly when a REM period is going to occur. This was an important consideration in designing the experiment described in Chapter 11.

TABLE 1

## CRITERIA FOR SLEEP STAGING

(after Rechtschaffen and Kales, 1968)

Stage	EEG	EMG tone	EOG Eye movements
Awake	alpha activity + low amplitude mixed frequency activity	high	occasional, rapid
<b>NREM</b>			
Stage 1	loss of alpha	reduced	slow
Stage 2	sleep spindles K complexes	reduced	absent
Stage 3	> 20% delta waves	reduced	absent
Stage 4	> 50% delta waves	reduced	absent
<b>REM</b>	low voltage, saw-toothed waves	markedly reduced	rapid

EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram. Alpha activity consists of waves at a frequency of 7-16 cycles per second. Sleep spindles are bursts of waves with a frequency of 12-14 cycles/sec. K complexes consist of a well defined sharp negative deflection in the EEG followed by a sharp positive deflection, the amplitude exceeding background EEG activity. Delta waves are high voltage slow waves (< 2 cycles/sec) and thus stages 3 and 4 are sometimes termed "slow wave sleep".

## 2. Measurement of arterial oxygen saturation using non-invasive techniques

Numerous authors have sampled blood intermittently during sleep from indwelling arterial catheters (Birchfield et al, 1958; Pierce et al, 1966; Atlan et al, 1968; Bristow et al, 1969; Interiano et al, 1972; Koo et al, 1975; Leitch et al, 1976; Flick and Block, 1977; Schroeder et al, 1978; Coccagna and Lugaresi, 1978; Guilleminault et al, 1980; Skatrud et al, 1981; Fletcher et al, 1983; Catterall et al, 1985). While this method allows accurate measurement of the tensions of both oxygen and carbon dioxide at separate time points, it is invasive, and it is a poor method of detecting transient changes.

Non-invasive measurement of arterial oxygen saturation by ear oximetry was first described in 1935 (Kramer, 1935; Matthes, 1935) and an oximeter designed by Millikan (1942) was used to study oxygenation during sleep in healthy individuals as early as 1952 (Doust and Schneider, 1952). However, these early models were relatively insensitive, they were difficult to calibrate, and they were cumbersome. It was not until the 1970's that accurate and reliable ear oximeters, suitable for clinical use, became available.

In all of the studies described in this thesis, the Hewlett Packard 47201A ear oximeter was used. This instrument measures the absorbance of light of eight different wavelengths transmitted through the ear, and then calculates the subjects' arterial oxygen saturation ( $\text{SaO}_2$ ) by relating these measurements to the absorbance characteristics of each wavelength at known values of  $\text{SaO}_2$ . A

number of authors have shown this device to be accurate (Saunders et al, 1976; Chaudhary and Burki, 1978; Douglas et al, 1979b; Ries et al, 1984) irrespective of normal variations in skin pigment (Saunders et al, 1976), and to have a rapid time response (Douglas et al, 1979b; Rebuck et al, 1983). In the largest of these studies, Douglas and colleagues (1979b) in this laboratory compared the arterial oxygen saturation measured by this instrument with measurements in simultaneously sampled arterial blood, from both normal subjects and patients with chronic bronchitis and emphysema, on 465 occasions. They found that, provided the  $\text{SaO}_2$  was greater than 65 percent, and the carboxyhaemoglobin concentration less than 3 percent, the ear oximeter measured  $\text{SaO}_2$  within 95 percent confidence limits of  $\pm 4$  percent. Changes in  $\text{SaO}_2$  in an individual are probably measured more accurately than this (Ries et al, 1984).

Although the ear oximeter measures arterial oxygen saturation accurately and continuously during the night, there is no general agreement on the most appropriate way of expressing this data, for it is unclear which parameters of nocturnal oxygenation are the most important in pathophysiological terms. The measurements that have been used by different authors include: the lowest  $\text{SaO}_2$  and maximal fall in  $\text{SaO}_2$  during sleep (Flick and Block, 1977; Douglas et al, 1979a; Stradling and Lane, 1983), the mean fall in  $\text{SaO}_2$  during sleep (Stradling and Lane, 1983), the number of 10 percent falls in  $\text{SaO}_2$  (Douglas et al, 1979a), the number of 4 percent falls in  $\text{SaO}_2$  (Block et al, 1979), the mean baseline  $\text{SaO}_2$  during sleep (Douglas et al, 1979a), and the percentage of time a patient's  $\text{SaO}_2$  is below a given

value (Weil et al, 1978; Wynne et al, 1979). However, none of these parameters alone adequately expresses all aspects of the oxygenation profile (Slutsky and Strohl, 1980). In this thesis, therefore, as in most previous papers, more than one measurement was made from the oxygenation trace of each patient. The measurements chosen were the  $\text{SaO}_2$  when awake and supine, the number of 4 percent falls in  $\text{SaO}_2$ , and the lowest  $\text{SaO}_2$  during sleep (see chapter 4).

### 3. The study of breathing patterns during sleep

In many studies of breathing during sleep, measurements of tidal volume have been made using either a mouthpiece and noseclip, or a facemask (reviewed by Douglas, 1982d). Although theoretically these methods provide the most accurate means of assessing ventilation, they suffer from a number of inherent errors including some which are particularly relevant to sleep. First, both systems may modify the depth and pattern of ventilation (Gilbert et al, 1972; Askanazi et al, 1980). Second, leaks may occur, especially during sleep as facial muscle tone decreases and patients move during sleep. Third, these systems may be cumbersome and uncomfortable and are therefore likely to interfere with sleep itself (Krieger and Kurtz, 1983). Douglas and colleagues (1982a-d) have recently developed a tight-fitting facemask with built-in leak detectors that is suitable for detailed studies of the physiology of breathing during sleep (Douglas et al, 1982a-c; Hudgel et al, 1984a, b; White et al, 1983, 1985), but this equipment requires constant checks for leaks and is unnecessarily sophisticated for most clinical studies.

The study of breathing patterns by methods which do not involve physical connection to the airway are more acceptable to the subject being studied, and thus probably interfere less with sleep and breathing patterns than either facemasks or mouthpieces and noseclips. Many methods are available and they have been reviewed by Sackner (1980). In the studies in this thesis, air flow was detected by thermocouples, and thoracic movement was measured semi-quantitatively by magnetometry.

**3(i) Detection of airflow by thermocouples:** Thermocouples placed in the path of airflow from the nose and mouth register the temperature of respired gas. They can distinguish warm expired gas from the cooler ambient air but they would not be expected to be sensitive indicators of expired volume. In practice we have found that respiration can virtually cease before thermocouple output diminishes. Thus thermocouples can be used to detect apnoea but are not useful for detecting smaller changes in ventilation (Catterall et al, 1983).

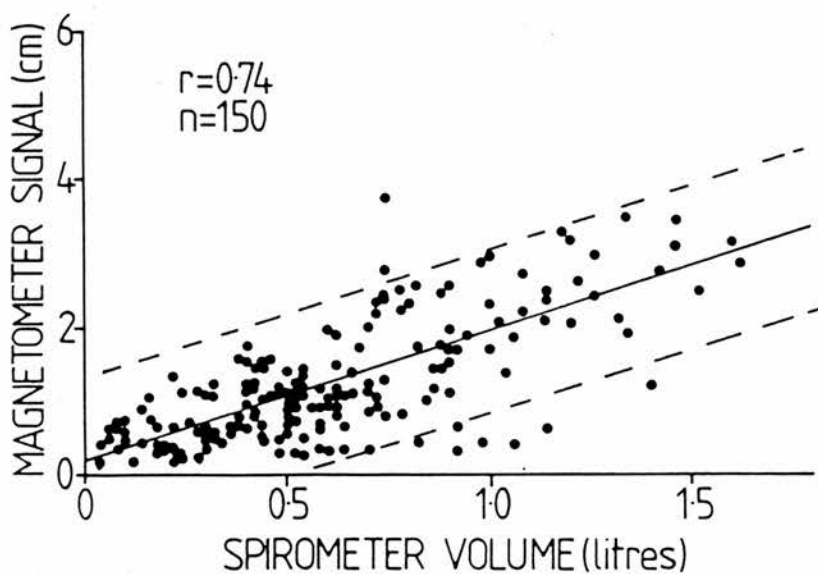
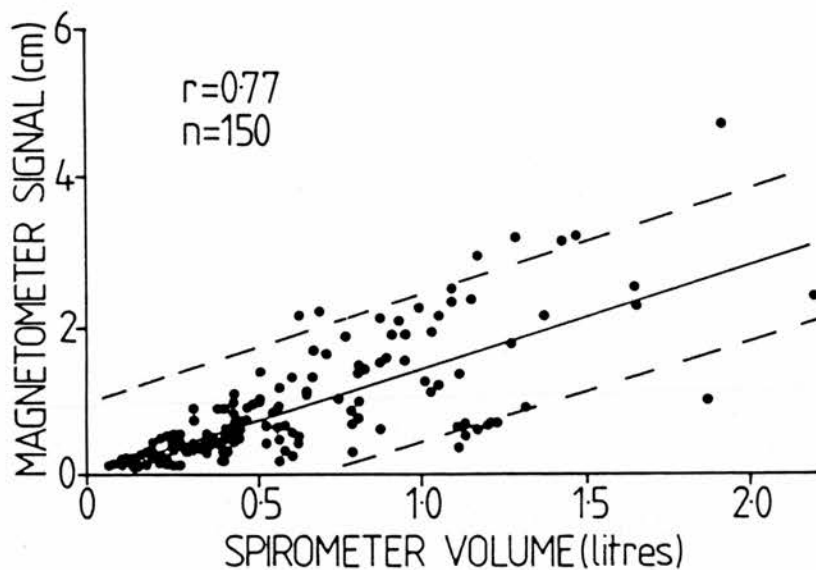
The respiratory magnetometer, however, can be used to provide semi-quantitative measurements of tidal volume.

**3(ii) Assessment of thoracic movement by magnetometry:** The respiratory magnetometer, developed by Mead and associates (1967), is a convenient method for studying breathing during sleep both in adults (Mortola and Anch, 1978; Tusiewicz et al, 1977; Sharp et al, 1980; Lopata and Onal, 1982; Skatrud et al, 1982; Goth et al, 1982;

Catterall et al, 1983; Skatrud and Dempsey, 1985) and in children (Bryan, 1979; Hagan et al, 1977). One coil of the magnetometer, placed on the anterior surface of the thorax, generates a magnetic field which is detected by another coil placed on the posterior surface of the thorax. The output voltage is proportional to the strength of the magnetic field which in turn varies with the cube of the distance separating the transmitting and sensing coils (Sharp et al, 1975). Since tidal volume is determined by movements of two compartments - the rib cage and abdomen (Kono and Mead, 1967) - and since tidal volume changes in these two compartments are linearly related to changes in their anteroposterior diameters (Kono and Mead, 1967), the chest magnetometer can be used to measure tidal volume quantitatively, provided that the relative contributions of chest and abdominal compartments do not change throughout the measurement period.

In this thesis, breathing was assessed by a magnetometer placed at the level of the third intercostal space anteriorly. The linearity of the magnetometer with respect to expired volume was assessed in two normal subjects, a 29 yr old man and 28 yr old woman (fig 1). The subjects wore a noseslip and breathed through a mouthpiece connected by low resistance respiratory tubing to an Ohio 670 Wedge Spirometer, while wearing magnetometer coils secured with adhesive tape. The spirometer was calibrated using a 1 litre gas syringe and both magnetometer and spirometer outputs were recorded on a Bryans 28000 time-based recorder.





**Fig 1** Comparison of magnetometer signal with spirometer volume for 150 breaths in each of two normal subjects. The regression (solid) line and 95% confidence limits for the measurements (dashed lines) are indicated.

Recordings were made of 150 breaths in five series each of 30 breaths. The first series was with the subject supine, the second in the left lateral position, the third supine, the fourth in the right lateral position, and the fifth supine once more. This allowed assessment of posture dependence and whether the calibration returned to its previous level when a given posture was resumed. Care was taken not to dislodge the magnetometer coils as the changes in posture were made. The majority of measurements were made in the supine posture because most subjects spent most of the night in that position.

In both subjects, there was a highly significant linear correlation ( $r = 0.77$  and  $0.74$ , both  $p < 0.001$ ) between the magnetometer signal and the spirometer measured volume (fig 1). When only data obtained in the supine posture was used, the correlations were improved ( $r = 0.91$  and  $0.79$  respectively, both  $p < 0.001$ ).

Thus the thoracic magnetometer gives a reasonably good index of expired volume in awake subjects. During sleep, however, the use of the chest magnetometer to measure tidal volume is complicated by two problems:

First, we have observed that posture changes can sometimes cause major changes in the calibration of the magnetometer and that these calibration changes can persist after the body movement has ceased. These sudden changes in calibration produced by alterations of posture are easily recognised from the magnetometer signal but they

mean that changes in the amplitude of chest movement during sleep can only be assessed during periods when there are no major changes in posture.

Second, the relative contributions of thorax and abdomen to tidal breathing do change during sleep. Mosso (1878) first reported that the thoracic contribution increased during sleep, a finding subsequently confirmed by Shepard (1914) but not by Reed and Kleitman (1926) or Magnussen (1944). Studies performed with EEG sleep staging have all shown that the thoracic contribution to tidal volume is increased in NREM sleep compared to wakefulness (Goldie and Green, 1961; Timmons et al, 1972; O'Flaherty et al, 1973; Tusiewicz et al, 1977; Mortola and Anch, 1978; Stradling et al, 1985), the largest study in adults (Gothe et al, 1981) showing a significant increase in the ratio of rib cage to total measurement from  $38 \pm 4$  (SE)% in wakefulness to  $49 \pm 4$ % in NREM sleep. During REM sleep, however, intercostal muscle tone is reduced (Tusiewicz et al, 1977; Tabachnik et al, 1981a), and the relative contribution of the rib cage falls again (O'Flaherty et al, 1973; Tusiewicz et al, 1977, Mortola and Anch, 1978; Tabachnik et al, 1981; Stradling et al, 1985). In all but the smallest of these studies (Tusiewicz et al, 1977), the thoracic contribution to tidal volume in REM sleep was similar to that in wakefulness.

In view of the changing thoracic contribution in different sleep stages, wide limits had to be set to ensure that differences in anteroposterior chest movement reflected differences in ventilation.

In this thesis, therefore, I have defined hypopnoea as a reduction of 50% or more in the amplitude of chest wall movement from the previous stable baseline during sleep, lasting for at least 10 seconds, and hyperpnoea as at least a doubling of the amplitude of chest wall movement for 10 seconds or longer (see Chapter 4).

In recent years, many investigators have used the respiratory inductive plethysmograph (Milledge and Stott, 1977; Sackner, 1980) to measure tidal volume during sleep. In theory, this device avoids the problem of changing thoracic and abdominal contributions for it allows measurement of both rib cage and abdominal movements simultaneously (Sackner, 1980). Inaccuracies due to posture changes during sleep are not abolished by use of this instrument, however (Zimmerman et al, 1983; Stradling et al, 1984). The studies described in this thesis were commenced before the respiratory inductive plethysmograph became popular and for the sake of consistency the chest magnetometer was used throughout.

#### **4. Assessment of airway calibre at night**

Whereas breathing patterns and arterial oxygen saturation can now readily be studied during sleep, it remains difficult to measure airway calibre while patients are asleep. Lopes and colleagues (1983) recently measured transpulmonary resistance during sleep in five normal volunteers, using an oesophageal balloon to measure pressure and the differentiated signal of a respiratory inductive plethysmograph to obtain flow. However, this study did not distinguish resistance in the bronchial tree from upper airway

resistance. Furthermore, the measurement of flow using a respiratory inductive plethysmograph has been shown to produce a noisy signal even in awake immobile subjects (Mannix et al, 1984). During sleep, this inaccuracy is likely to be increased because of body movement (Zimmerman et al, 1983) and because of changes in the phase relationship and relative contributions of the different components of the chest and abdominal wall (Tusiewicz et al, 1977; Mortola and Anch, 1978; Gothe et al, 1981; Tabachnik et al, 1981a, b). Hudgel and colleagues measured flow with a pneumotachograph attached to a tight fitting facemask during sleep. By placing an additional catheter in the retroepiglottic space, they also distinguished resistance changes above the larynx from those in the lower airway. They found no significant changes in lower airway resistance during sleep, but their measurements were made only in normal volunteers. Furthermore, sleep was severely disturbed in these studies, with some of the patients not even entering stage 3 or 4 sleep. Similar studies in asthmatic patients would be very difficult for they have disturbed sleep even without such instrumentation (see Section III). Similar studies have recently been attempted in our laboratory but with little success because of the subjects' disturbed sleep.

In this thesis, I used measurements of forced expiratory volume in one second ( $FEV_1$ ) and peak expiratory flow rate (PEFR) to study the relationship between bronchoconstriction and sleep. In order to relate these measurements to sleep or individual sleep stages, patients were woken from electroencephalographically documented sleep

and the measurements made immediately. The main drawback of this approach is that sleep - one of the variables under study - has to be disturbed in order for the measurements to be made. Another potential problem is that forced expiratory manoeuvres are effort-dependent, and it could be argued that patients who have just been woken from sleep may not be as well motivated to produce a maximal effort as they are during the day. This latter point is unlikely to be a major source of error, however, since circadian changes in peak flow can be demonstrated in patients who have not just been wakened and, furthermore, asthmatic patients often waken from sleep spontaneously because of wheeze.

Clearly it is not ideal to use  $FEV_1$  and PEF<sub>R</sub> measurements to study the relationship between bronchoconstriction and sleep. However, I believe that this approach does provide useful information and, to date, it is the only method of studying nocturnal bronchoconstriction that has been shown to be practicable in patients with asthma.

##### **5. Factors affecting sleep and breathing during sleep**

Strict criteria for sleep stages and breathing patterns, and accurate measurements of oxygenation and bronchoconstriction, allow reasonable comparisons to be made between sleep studies. Equally important, however, are the conditions under which sleep studies are performed, for many variables can affect the results. These include:

#### 5(i) The "first night" effect

Most investigators (Agnew et al, 1966; Mendels and Dawkins, 1967; Schmidt and Kaelbling, 1971; Webb and Campbell, 1979), but not all (Kader and Griffin, 1983), agree that the sleep of normal subjects (and therefore potentially any sleep-induced changes in breathing and oxygenation) is disturbed in unfamiliar surroundings, the duration and quality of sleep returning to normal on the second to fourth consecutive nights. For this reason all of the studies in this thesis were performed on two consecutive nights but data was collected only on the second night.

#### 5(ii) Time of study and shift work

In order to avoid the inconvenience of collecting data at night, some sleep studies, including one of the most comprehensive studies of breathing during sleep in normal subjects (Bulow, 1963), have been performed during daytime in night workers, including some who changed shifts frequently. Shift workers, however, especially those with frequent changes of shift (Dahlgreen, 1981), are sleep deprived and have abnormal patterns of sleep. Furthermore, sleep-deprivation can interfere with ventilatory responses (Cooper and Phillips, 1982; Schiffman et al, 1983; White et al, 1983). In this thesis, all of the studies were performed at night and none of the subjects worked shifts.

#### 5(iii) Commonly used drugs and drinks

Alcohol, benzodiazepines and coffee can each affect sleep and also breathing during sleep. It is important that this be taken into

account in the interpretation of studies of breathing and oxygenation during sleep.

Alcohol: Several workers have shown that alcohol increases the frequency and duration of apnoeas in patients with the obstructive sleep apnoea syndrome (Guilleminault et al, 1980; Issa and Sullivan, 1982; Scrima et al, 1982), although there is debate whether this occurs in healthy subjects (Taasan et al, 1981; Scrima et al, 1982). Dolly and Block (1982) also found a small but significant increase in the frequency and duration of sleep apnoea in patients with chronic obstructive lung disease who had taken alcohol, although episodes of hypopnoea and desaturation, which are much more common than apnoea in chronic obstructive airways disease (Catterall et al, 1983), did not increase.

Benzodiazepines: Benzodiazepine hypnotics can cause an increase in apnoea frequency and duration in normal subjects (Dolly and Block, 1982) and an increase in the duration and severity of arterial oxygen desaturation in patients with chronic obstructive lung disease (Block et al, 1984). Mendelson and colleagues (1981) described a 38 year old man with a history of snoring, insomnia and hypersomnolence who, after taking 30 mg of flurazepam for two nights, had an increase in the number of sleep apnoeas from 18 per night to 100 per night with an increase in daytime hypersomnolence.

Coffee: Coffee is a stimulant which decreases sleep and could therefore affect nocturnal breathing patterns and oxygenation



indirectly. Whether coffee affects breathing patterns during sleep by a direct mechanism is unknown, but it can act as a bronchodilator (Salter, 1859; Rall, 1980) and could almost certainly affect the interpretation of studies of bronchoconstriction.

In order to avoid the above problems we studied no subjects who were taking hypnotics and we instructed all the subjects to avoid alcohol and coffee on study nights.

## Part II

### **THE NORMAL RANGE OF IRREGULAR BREATHING AND OXYGENATION DURING SLEEP**

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### Chapter 3

#### REVIEW OF THE LITERATURE

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Most studies of breathing and oxygenation during sleep in healthy subjects have been concerned with the mechanism and control of breathing in different sleep stages (REM and NREM). These studies have been reviewed extensively (Phillipson, 1978; Douglas, 1985; Krieger, 1985). In contrast, relatively little is known of the normal variation in breathing and oxygenation during sleep among different individuals, or of the factors which influence that variation. It is important to know these variations since they provide important reference data for clinical studies, and they may also contribute to our understanding of the physiological factors which control breathing during sleep. In this chapter I shall review previous work on the normal inter-individual variation of breathing and oxygenation during sleep and the factors which account for that variation.

# 1. The normal range of irregular breathing and oxygenation during sleep

According to Guilleminault and colleagues (1978) a sleep apnoea syndrome is diagnosed if, during seven hours of nocturnal sleep, at least 30 apnoeic episodes are observed in both REM and NREM sleep, some of which have to appear repetitively in NREM sleep. This definition of the sleep apnoea syndrome has proved to be useful in clinical practice, and it is widely quoted and accepted. However, there remains uncertainty about the normal range of apnoea and hypopnoea during sleep.

The study on which the above definition was based included only 20 normal control subjects (Guilleminault et al, 1978). Furthermore, Guilleminault and colleagues (1978) gave relatively few details of those normal subjects, stating only that "they were 40 to 60 years of age and included subjects of both sexes." It is not clear how the subjects were distributed with regard to age or sex, nor how the authors defined normality. Also, this study involved no assessment of the amount of hypopnoea, yet authors from the same centre, in a different paper, diagnosed a sleep apnoea syndrome if patients had a total number of apnoeas plus hypopnoeas which exceeded 30. This confusion has been compounded by the fact that different groups have defined hypopnoea in different ways (Block et al, 1979; Guilleminault et al, 1980a, Catterall et al, 1983a).

Most patients with the sleep apnoea syndrome have many more than 30 apnoeas per night, so that diagnosis of this condition does not

usually present problems. When trying to determine the importance of sleep-disordered breathing in other diseases, however, (e.g. asthma or chronic bronchitis and emphysema) or in patients with ill-defined symptoms - where differences from normality are likely to be less marked - it is important to have more detailed reference data.

Block and colleagues (1979) questioned Guilleminault's definition of the sleep apnoea syndrome. Some of their asymptomatic subjects (Block et al, 1979) had frequent episodes of apnoea and/or oxygen desaturation during sleep, and the authors suggested that arbitrary separation of the sleep apnoea syndrome from normal at 30 apnoeic episodes per night was unwarranted. However, most of the irregular breathing and oxygen desaturation in the study by Block and colleagues occurred in four very obese subjects (see below). The normal range of apnoea, hypopnoea and oxygenation during sleep thus remains uncertain.

## **2. Factors which may account for the normal variation in breathing and oxygenation during sleep in healthy subjects**

### **2(i) Familial and genetic factors**

There are rare instances in which a sleep apnoea syndrome may run in families. Some well-known genetic disorders such as myotonic dystrophy predispose to sleep apnoea (Cumiskey et al, 1978), but other examples of familial sleep apnoea syndromes are less well understood (Strohl et al, 1978; Elliott, 1978; Walsh and Montplaisir,

1982). Guilleminault and colleagues (1986) recently reported five families, each with a history of "near miss" or actual sudden infant death syndrome, in which both children and adults had a small posterior airway at the level of the tongue.

Thus, it seems likely that genetic factors may occasionally increase susceptibility of patients to sleep apnoea. However, in most patients with abnormalities of breathing and oxygenation during sleep, there is no obvious hereditary element.

## **2(ii) Body weight**

Obesity is such a common disease that obese subjects are sometimes included in series of so-called normal subjects (Block et al, 1979; Block, 1986). This is inappropriate in studies of respiration during sleep, however, for obesity can undoubtedly affect sleep-induced breathing patterns and nocturnal oxygenation.

Many patients with the sleep apnoea syndrome are obese. It has been estimated that the sleep apnoea syndrome is at least 25 times more common among morbidly obese patients than among patients of normal weight (Peiser et al, 1984). Moreover, weight reduction in these patients, accomplished either by dieting (Guilleminault et al, 1978; Kerin et al, 1979; Browman et al, 1984) or by gastrointestinal bypass surgery (Peiser et al, 1984), causes a reduction in the number of sleep apnoeas per night. In 15 morbidly obese subjects with the sleep apnoea syndrome, Peiser and colleagues (1984), found a significant correlation ( $p < 0.025$ ) between the number of apnoeas per

hour of sleep and the percent excess weight. After weight reduction, however, there was no linear relation between the amount of weight lost and the decrease in apnoeas. Furthermore, most obese patients do not suffer from the sleep apnoea syndrome (Peiser et al, 1984), and approximately half of the patients with the sleep apnoea syndrome are within 20 percent of ideal body weight (Guilleminault et al, 1978; Sullivan and Issa, 1985).

In summary, obese subjects are more likely to have the sleep apnoea syndrome than non-obese subjects, although there is no clear cut relationship between body weight and the incidence of sleep apnoea.

## 2(iii) Sex

Most patients with the sleep apnoea syndrome are men (Guilleminault et al, 1978; Sullivan and Issa, 1985), and it has been suggested that there may be a fundamental sex difference in breathing and oxygenation during sleep (Block et al, 1979). However, there is insufficient published data to know whether this is correct.

Although numerous studies of respiration during sleep have included both male and female subjects (Smith, 1860; Ostergaard, 1944; Doust and Schneider, 1952; Birchfield et al, 1959; Bulow, 1963; Duron, 1972; Snyder et al, 1974; Block et al, 1979; Ancoli-Israel et al, 1981; Carskadon and Dement, 1981; Smallwood et al, 1983), relatively few publications (Bulow, 1963; Block et al, 1979; Ancoli-Israel et al, 1981; Carskadon and Dement, 1981; Smallwood et al, 1983) have contained sufficient data for a formal comparison to be made between

the sexes, and only three of these (Bulow, 1963; Block et al, 1979; Guilleminault et al, 1978) have included subjects under the age of 50 years.

Bulow (1963) in his study of respiration during sleep in 31 men and 22 women observed periodic breathing in most of the subjects studied, but found no sex difference in either the severity or incidence of periodic breathing. However, the subjects were studied during the day and therefore probably slept poorly, and detailed observations on breathing pattern were made only during sleep onset. Furthermore the measurements were made with a mouthpiece and noseclip, which may be inaccurate during sleep (see Chapter 2). Bulow observed that ventilation in REM sleep was highly variable but no data was given for either sex, and there were no measurements of oxygenation in that study.

Block and colleagues (1979), using surface measurements to monitor breathing patterns and ear oximetry to measure oxygenation, studied breathing during sleep in 49 "normal" adults, of whom 30 were men. Apnoea occurred in 3 of the 19 women and in 12 of the 30 men. Desaturation (falls in arterial oxygen saturation of greater than 4 percent from the preceding base line) did not occur in the women, but 251 episodes of desaturation, in 17 subjects, were observed in the men, most of these hypoxaemic episodes being associated with either hypopnoea or apnoea. The authors concluded that sleep apnoea, hypopnoea and oxygen desaturation occur in normal subjects and that these findings are "almost exclusively male characteristics."



However, there were important differences between the men and women studied which could have affected the results. Most of the irregular breathing and hypoxaemia in that study occurred in four very obese men. The men were also older than the women, and there is evidence that irregular breathing during sleep may increase with age (see below). Furthermore, the men were more hypoxaemic than the women even when awake and thus were predisposed to greater falls in arterial oxygen saturation since they started the night on a steeper part of the oxyhaemoglobin dissociation curve (Catterall et al, 1983; Stradling and Lane, 1983). It is possible, therefore, that some of the observed differences between the male and female groups in that study could have been due to variables other than the subjects' sex.

The study by Guilleminault and colleagues (1978) also included separate data for the two sexes. They monitored 20 normal control subjects, between 40 and 60 years of age, over four consecutive eight-hour nocturnal sleep periods, and found that the mean number of apnoeic episodes per night was 7 (range 1-25) in the men and 2.1 (range 0-5) in the women. It is unclear whether these differences were significant, however, for the authors gave no further details of the results or of the subjects studied.

Neither Ancoli-Israel and colleagues (1981) nor Carskadon and Dement (1981) found a sex difference in breathing patterns during sleep, but these studies were performed exclusively on subjects over 62 years of age. Furthermore, although the latter investigation is usually quoted as an example of a study of normal individuals, the subjects

were selected for study only if they had a history suggestive of sleep apnoea. Smallwood and colleagues (1983) found apnoea and hypopnoea during sleep to be more prevalent in elderly men than in elderly women, but only 6 normal female subjects took part in that study compared with a total of 35 women in the two earlier studies. In none of these three studies of the elderly was oxygenation measured.

In summary, there have been no detailed studies of breathing and oxygenation during sleep in which healthy non-obese men have been compared with healthy non-obese women over a wide age spectrum. In previous work suggesting a fundamental sex difference in respiration during sleep, the men and women were poorly matched for age, body weight and oxygenation when awake, whereas the studies which showed no sex difference in respiration during sleep were all performed on elderly subjects.

## **2(iv) Age**

Breathing during sleep in children differs from that in adults because the central nervous system, respiratory muscles, and osteochondral structures are not fully developed. These differences from adults are particularly marked in the newborn, and have been reviewed elsewhere (Henderson-Smart and Read, 1978; Ariagno and Guilleminault, 1985).

In adults, Bulow (1963) found that the incidence and severity of periodic breathing during sleep were not related to age. However,

as noted above, these observations were made only during sleep onset. Webb (1974), in contrast, using a loose-fitting facemask, observed periodic breathing with episodes of apnoea in 9 of 11 normal subjects over the age of 45 years but in none of the subjects under 45 years.

Carskadon and Dement (1981) used surface measurements to study breathing patterns during sleep. They studied 40 elderly volunteers aged 62 - 86 years and compared their results with those from 20 younger subjects aged 40 - 60 years who had been studied in the same laboratory several years earlier (Guilleminault et al, 1978). They concluded that the elderly subjects had many more "respiratory events" during sleep than the younger subjects and that 15 of the 40 normal volunteers had a sleep apnoea syndrome. However, the authors were not justified in drawing this conclusion from the data presented, for a respiratory event was defined differently in the two studies: in the elderly subjects the number of respiratory events was taken as the number of apnoeas plus the number of hypopnoeas, whereas in the younger subjects Guilleminault and colleagues (1978) had counted only the number of apnoeas.

In none of the foregoing studies comparing older and younger subjects was nocturnal oxygenation measured. Block and colleagues (1979) found that falls in arterial oxygen saturation during sleep became more frequent with increasing age. However, this initial study did not include any women over the age of 51 years, and the average age of the female subjects studied was only 29 years. In a subsequent study (Block et al, 1980), the same group studied breathing and

oxygenation during sleep in postmenopausal women and compared the results with those of their initial study. They found that postmenopausal women resembled men in having more falls in arterial oxygen saturation than premenopausal women, i.e. the premenopausal women appeared to be protected from irregular breathing and hypoxaemia during sleep. The authors suggested that this might be due to the higher levels of circulating progesterone in the premenopausal women. However, the premenopausal women also differed from the men and the postmenopausal women in a number of other respects, each of which could have affected the results of those studies. The premenopausal women were on average 18.5 kg lighter than the men and they were both less heavy and less tall than the postmenopausal women. They also slept for a shorter length of time than the other subjects and they had a higher arterial oxygen saturation when awake than either the men or the postmenopausal women. This last difference between the premenopausal women and the other subjects would have affected not only the nocturnal oxygen saturation (the premenopausal women being less likely to desaturate because of their position at the start of the night on a flatter part of the oxyhaemoglobin dissociation curve) but also the authors' estimate of the amount of irregular breathing, for Block and colleagues (1979) diagnosed hypopnoea only if the change in breathing pattern was accompanied by a significant (4 percent or greater) fall in saturation.

In summary, these studies suggest that older subjects are more likely to have irregular breathing and oxygen desaturation during sleep than

younger subjects, but this has not been proved conclusively, partly because of the methodological problems (including different definitions of hypopnoea by different groups) and partly because some studies included grossly obese subjects whose ages were not given. The results of Block and colleagues (1979) suggest that the effect of age may be more marked in women than in men but this also remains unproven.

In order to clarify the effects of age and sex on respiration during sleep in healthy subjects, and to determine a normal range of irregular breathing and hypoxaemia during sleep, I performed studies on 40 non-obese healthy adults, who covered a wide age spectrum in both sexes.

## Chapter 4

### **STUDIES OF BREATHING AND OXYGENATION DURING SLEEP IN NON-OBESE HEALTHY SUBJECTS**

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This study was performed in order to establish a normal reference range for irregular breathing and oxygenation during sleep in our laboratory, and also to investigate the effects of age and sex on respiration during sleep in non-obese subjects.

#### METHODS

##### Subjects

Volunteers were sought, and all were studied if they were non-obese. None of the volunteers experienced daytime somnolence nor did they report disturbed nocturnal sleep. Twenty of the subjects (10 M, 10 F) were younger than 45 years and 20 (9 M, 11 F) were older than 45 years (table 2). The 10 women younger than 45 yr were all premenopausal and the 11 women over 45 yr were all at least 2 years postmenopausal, 10 after natural menopause and 1 (a 46 yr old woman) after a hysterectomy and bilateral salpingo-oophorectomy 3 years previously. None of the subjects had present or previous evidence of cardiorespiratory disease and, although 5 (3 M, 2 F) were smokers and 4 (2 M, 2 F) were ex-smokers, all had normal FEV<sub>1</sub>, FVC, chest

**Fig 2** Illustration of subject under study, showing electroencephalographic, electromyographic and electro-oculographic leads, ear oximeter, thermocouples on nasal prongs and magnetometer (white). The black sensor above the magnetometer is a transcutaneous oxygen electrode which was used in some studies, but proved to be inaccurate.

radiograph, and ear oxygen saturation when awake. No subject was receiving hypnotic, sedative or stimulant drugs. Four of the premenopausal women were taking contraceptive pills, and 3 subjects older than 55 yr (2 M, 1 F) were receiving hypoglycaemic agents orally for maturity onset diabetes, but none had evidence of either peripheral or autonomic neuropathy (Catterall et al, 1984). All the subjects studied were within 12% of average body weight (Documenta Geigy, 1970).

As in all studies described in this thesis, each subject gave informed consent to the study, which had the approval of the South Lothian Division of Medicine Ethical Advisory Committee.

### **Procedure**

The subjects slept in a quiet darkened room on 2 consecutive nights (fig 2). The first night was for acclimatisation, and data were collected only on the second night. Air flow was recorded at the nostrils and mouth by thermocouples mounted on nasal prongs, anteroposterior chest wall movement was recorded by magnetometer coils at the level of the third intercostal space anteriorly, and arterial oxygen saturation ( $\text{SaO}_2$ ) was recorded by the Hewlett-Packard 47201A ear oximeter (Hewlett-Packard, Waltham, MA) (Douglas et al, 1979b). Electroencephalogram (EEG) was recorded by 2 midline frontoparietal electrodes, electrooculogram (EOG) by 4 electrodes outside and above the outer canthi and electromyogram (EMG) by 2 submental electrodes.



TABLE 2

## DEMOGRAPHIC DATA OF NORMAL SUBJECTS STUDIED

Female Subjects				
	Premenopausal (n = 10)		Postmenopausal (n = 11)	
	Mean	Range	Mean	Range
Age (yr)	29	22-42	55	45-64
Body weight (% average)	100	85-105	97	87-112
SaO <sub>2</sub> awake (%)	97	95-99	96	95-98
Male Subjects				
	Younger than 45 yr (n = 10)		Older than 45 yr (n = 9)	
	Mean	Range	Mean	Range
Age (yr)	31	23-42	55	45-68
Body weight (% average)	98	87-104	98	88-105
SaO <sub>2</sub> awake (%)	97	95-99	96	94-98

Average body weight data derived from Documenta Geigy, 1970.



**Fig 2** Illustration of subject under study, showing electroencephalographic, electromyographic and electro-oculographic leads, ear oximeter, thermocouples on nasal prongs and magnetometer (white). The black sensor above the magnetometer is a transcutaneous oxygen electrode which was used in some studies, but proved to be inaccurate.

Once this equipment had been attached (approximately 11.15 pm), the subject lay awake for 15 minutes, during which time data were collected. Thereafter, the lights were switched off ("lights out") and the subject was allowed to sleep. Unless assistance was sought from the doctor and/or nurse present, the subjects were not disturbed until 6.30 am. After final awakening ("lights on") at least 15 minutes of data were obtained before the monitoring equipment was removed.

The  $\text{SaO}_2$ , breathing patterns, and EEG traces were recorded on separate time-based recorders synchronised by a computer-generated time code every 15 minutes. EEG, EOG and EMG were recorded on an SLE E8b recorder running at 15 mm/sec. Arterial oxygen saturation, air flow and chest wall movements were displayed on a Mingograff 81 recorder running at 5 mm/sec. To allow easier identification of long term shifts in oxygenation, saturation was also recorded on a Bryans 28000 recorder at 30 mm/hr. I analysed all breathing and oxygenation traces without knowledge of the age or sex of the subject under study and the breathing trace was analysed without knowledge of the oxygenation record and vice versa. Both were analysed without knowledge of the EEG sleep stage. Breathing patterns and oxygenation during periods of wakefulness were excluded from the final analysis as the aim of the study was to examine respiration during sleep itself and also because subjects tended to be restless if they woke transiently during the night, making analysis and interpretation of the traces difficult at those times.

### Analysis of sleep duration and quality

The EEG, EOG and EMG traces were kindly analysed by Dr C M Shapiro from the Department of Psychiatry, University of Edinburgh. The traces were analysed by standard criteria (Rechtschaffen and Kales, 1968; table 1) in 20-second epochs, and the following variables determined:

Time in bed (or total recording time), from "lights out" to "lights on".

Sleep period time, from sleep onset (the onset of the first epoch of stage 2 sleep) to final awakening.

Total sleep time, this being the total time spent in EEG sleep stages 1, 2, 3, 4 and REM.

Sleep efficiency index, a calculation of the total sleep time divided by the time in bed.

Sleep onset latency, this being the time from "lights out" to sleep onset.

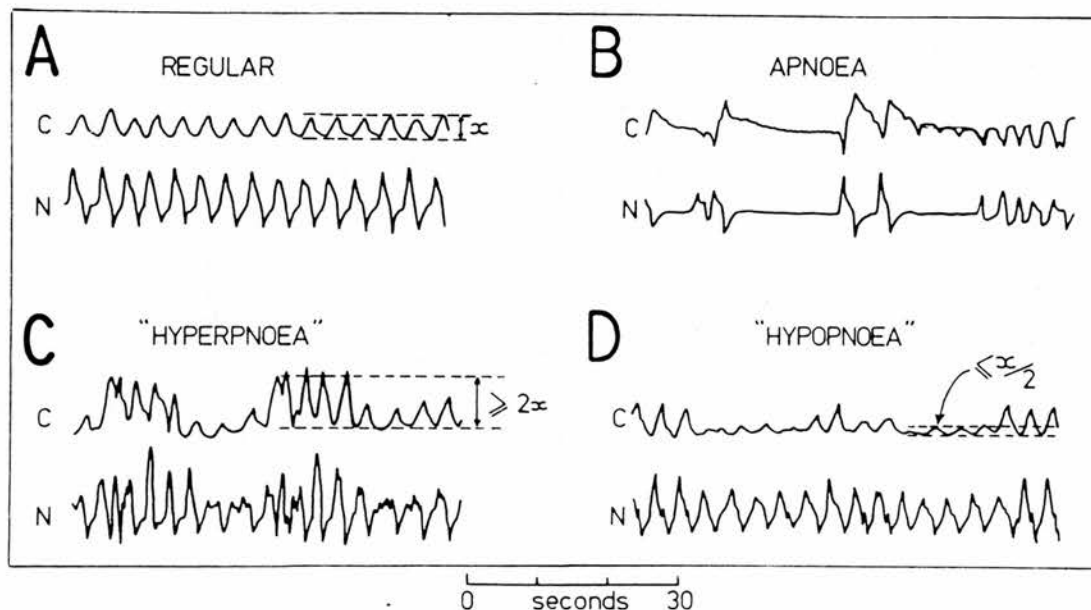
The cumulative duration of each sleep stage, expressed both in minutes and as a percentage of the total sleep time.

### Analysis of breathing patterns (fig 3)

The breathing pattern traces were analysed for:

Apnoea, defined as cessation of air flow at the mouth and the nostrils for at least 10 seconds, and classified as obstructive or central by conventional criteria (Guilleminault et al, 1976; fig 3).

Hypopnoea, in which, despite continued air flow, the amplitude of the magnetometer signal fell to less than 50% of the level during the



**Fig 3** Classification of breathing patterns.  
 C = chest wall movement; N = airflow at nostril.  
 x is the amplitude (in arbitrary units) of the chest wall movement in a subject during stable regular breathing while asleep. In B, an episode of obstructive apnoea (in which chest wall movement continues despite cessation of airflow) is shown following an episode of central apnoea (in which both airflow and chest movement cease).

immediately preceding regular breathing, for every breath during at least 10 seconds (fig 3).

Hyperpnoea, in which the amplitude of the magnetometer signal doubled for at least 10 seconds with continued air flow (fig 3).

Over 95% of episodes of apnoea, hypopnoea or hyperpnoea occurred repetitively, giving easily recognised periods of irregular breathing. Such a period was defined as starting with either an apnoea, a hypopnoea, or a hyperpnoea, and ending at the beginning of the next 2 minute period in which there was uninterrupted regular breathing. The total duration of irregular breathing in each subject was the sum of all these periods.

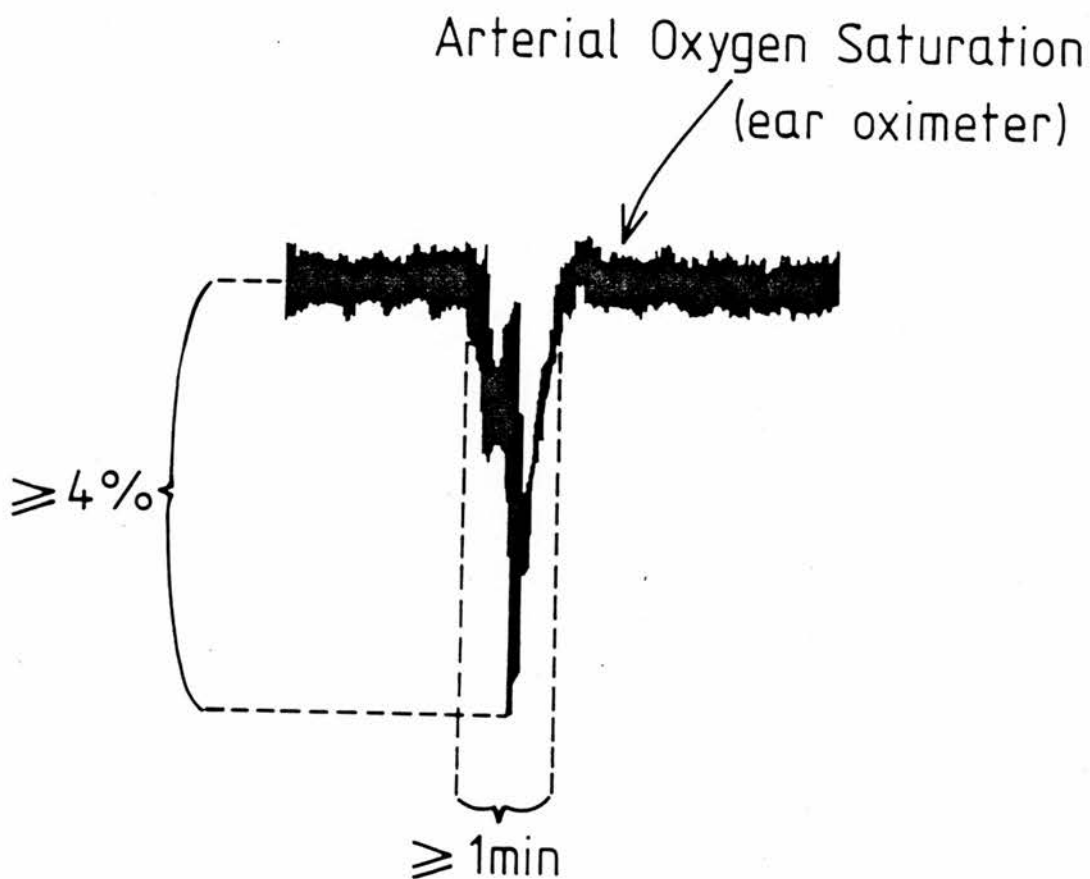
#### Analysis of arterial oxygen saturation

The following data were obtained from each oxygen saturation trace:

Awake saturation, this being the average of the pre and post sleep values, there being no significant difference between these values. This value thus reflected at least 30 min of EEG confirmed wakefulness, normally longer depending on sleep onset latency and the time of final awakening, during which the subject was supine.

The lowest oxygen saturation during sleep, readings below 65% being corrected to allow for the fact that the Hewlett-Packard ear oximeter underestimates  $\text{SaO}_2$  at these levels (Douglas et al, 1979b).

The number of hypoxaemic episodes A hypoxaemic episode was defined as a fall in arterial oxygen saturation of more than 4% from the immediately preceding stable saturation during sleep, such a fall lasting at least 1 min (fig 4).



**Fig 4** Definition of a hypoxaemic episode. A hypoxaemic episode was defined as a fall in arterial oxygen saturation (ear oximeter) of more than 4% from the immediately preceding stable saturation during sleep, lasting at least 1 min.

Results are quoted as mean  $\pm$  standard error or as mean and range. The significance of observed differences between sexes and between age groups was assessed by the unpaired "t" test (Documenta Geigy, 1970).

## RESULTS

Individual examples of the oxygen saturation traces and EEG sleep stages obtained in four subjects are shown in fig 5.

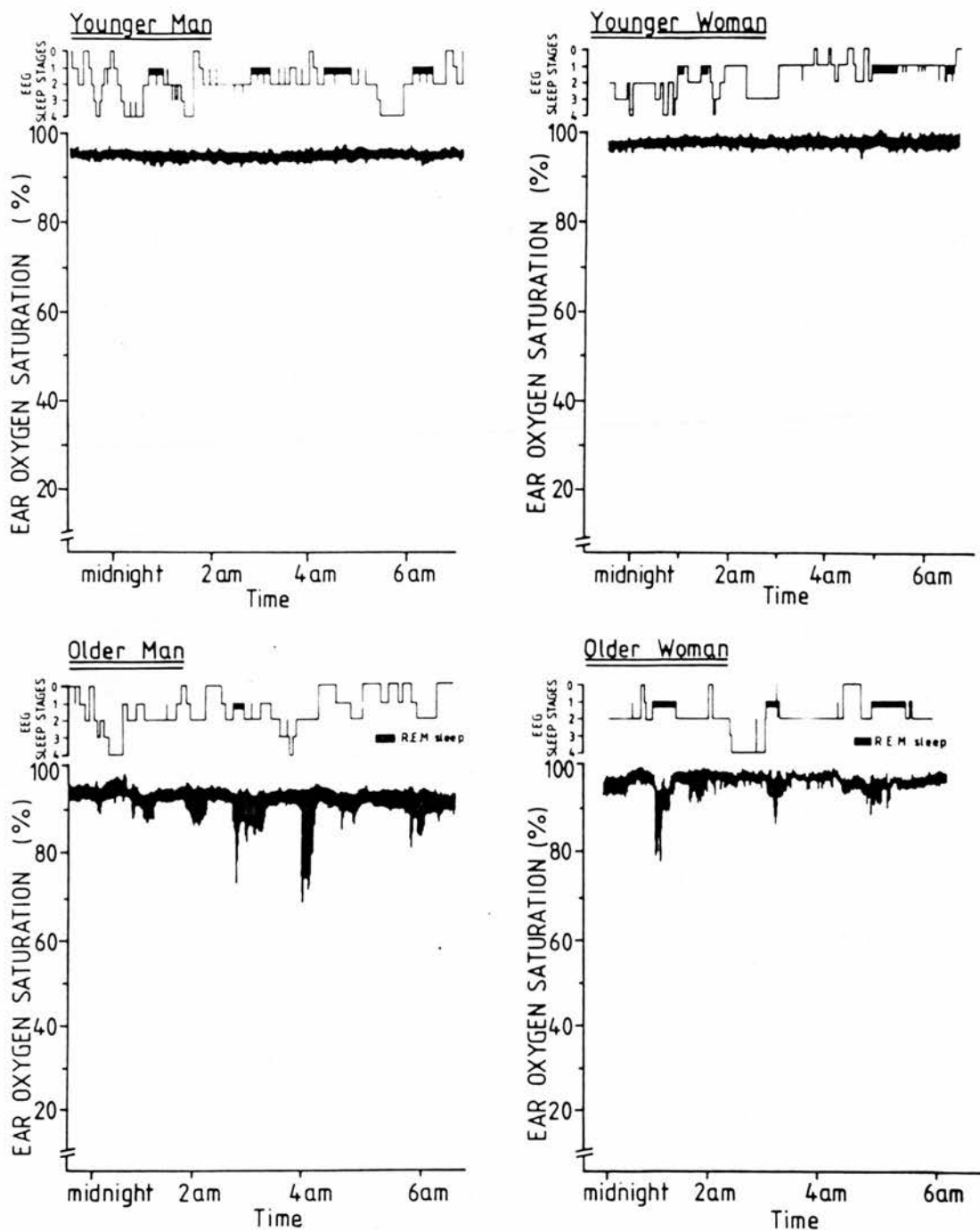
The results for all the subjects are summarised in table 3 and in figures 6 and 7.

The data for the subjects individually are shown in the appendix. Tables 11 and 12 (appendix) contain the data on sleep duration and quality, tables 13 and 14 the data on breathing patterns, and tables 15 and 16 the data on oxygenation.

### Sleep duration and quality

Time in bed averaged 7 h 6 min with no significant difference between the men and the women or between the older subjects (aged 45 yr or more) and the younger subjects (under 45 yr; table 3). Total sleep time averaged 6 h 17 min of which 81% (range 69 to 98%) was NREM sleep and 19% REM sleep. There was no sex difference in the total sleep time or the duration of individual sleep stages (table 3). However, the men and women over 45 yr of age slept less well than





**Fig 5** Examples of arterial oxygen saturation (ear oximeter) and EEG sleep stages throughout the night in 4 non-obese healthy subjects. Top left, a 23 year old man; top right, a 22 year old woman; bottom right, a 68 year old man; bottom left, a 63 year old woman.



**Footnot to table 3**

In subject 1, the EEG, EOG and EMG traces were of poor quality and no sleep data was analysed. For the sleep data only, therefore,  $n = 20$  for female subjects and  $n = 19$  for the subjects under 45 yr. For data on individual subjects, see appendix (tables 11-16).

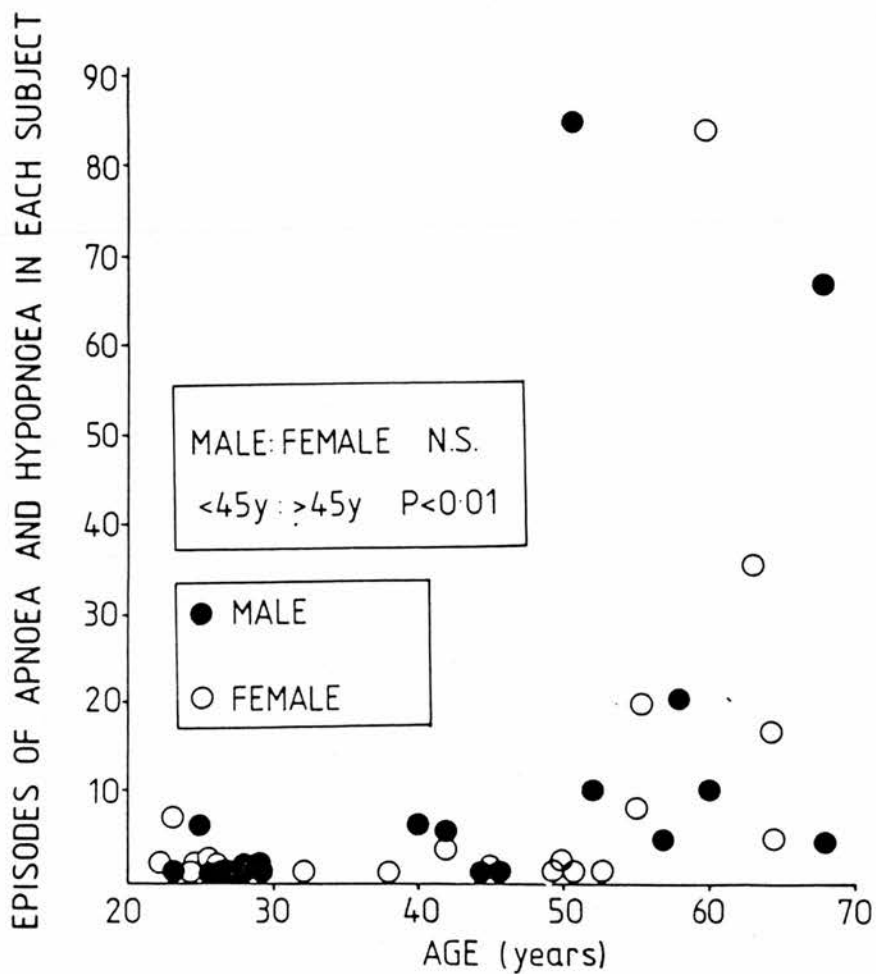
those younger than 45 yr, with a shorter total sleep time ( $p < 0.02$ ) and less time spent both in stage 3 sleep ( $p < 0.01$ ) and stage 4 sleep ( $p < 0.01$ ) than the younger subjects (table 3). The duration of REM sleep was similar in the older and younger subjects (table 3).

### **Breathing patterns**

Episodes of hyperpnoea were very uncommon, occurring in only 3 subjects 1 to 3 times per night. They were not associated with any significant EEG or  $\text{SaO}_2$  change, and hyperpnoea is therefore not considered further.

There was no difference between men and women in either the number of apnoeas per night, the number of episodes of hypopnoea per night or the sum of these in each subject (fig 6, table 3). Apnoea tended to occur more frequently in the subjects older than 45 yr than in those younger than 45 yr but there was a wide range of values, especially in the older subjects (appendix, tables 13, 14) and the difference did not reach statistical significance (table 3). However, the number of hypopnoeas ( $p < 0.01$ ), the total number of apnoeas and hypopnoeas ( $p < 0.01$ ) and the duration of irregular breathing ( $p < 0.01$ ) were each significantly greater in the subjects over the age of 45 yr than in those under 45 yr (fig 6; table 3). Almost all (168 of 179) of the apnoeic episodes recorded were obstructive. There was no difference in any of these parameters of irregular breathing between the men and women in either age group (table 3).

Two subjects (a 51 yr old man and a 60 yr old woman) had more than 30



**Fig 6** Number of episodes of apnoea and hypopnoea per night in relation to each subject's age and sex, showing that the number of episodes increases with age but that there is no difference between the sexes.

apnoeas per night. In a further two subjects (a 63 yr old woman and a 68 yr old man), the total number of apnoeas plus hypopnoeas exceeded 30 (Guilleminault et al, 1978; Carskadon and Dement, 1981; fig 6).

Three subjects described themselves as snorers. These were a 51 yr old man with 45 apnoeas and 40 episodes of hypopnoea, a 52 yr old man with 2 apnoeas and 8 episodes of hypopnoea and a 63 yr old woman with 1 apnoea and 35 hypopnoeas. These three snorers did not have significantly more irregular breathing than the other 37 subjects and the difference in irregular breathing between the older subjects and younger subjects remained significant if the three smokers were excluded.

#### Arterial oxygen saturation

Arterial oxygen saturation when awake averaged 97% (range 94 to 99%), with no significant difference between the men and the women (table 3). There was also no sex difference in either the number of hypoxaemic episodes per subject or the lowest  $\text{SaO}_2$  recorded during sleep in each subject (fig 7, table 3). In both sexes there was a tendency for the arterial oxygen saturation to fall with increasing age, especially during sleep (fig 7). The lowest  $\text{SaO}_2$  during sleep averaged 89% (range 71 to 95%) in the men and women older than 45 yr and 93% (range 90 to 96%) in those younger than 45 yr ( $p < 0.02$ ; fig 7, table 3). Almost all (26 of 28) of the hypoxaemic episodes occurred in the 20 older subjects, the majority (19 of 28) in subjects older than 60 yr of age. However, the subjects older than

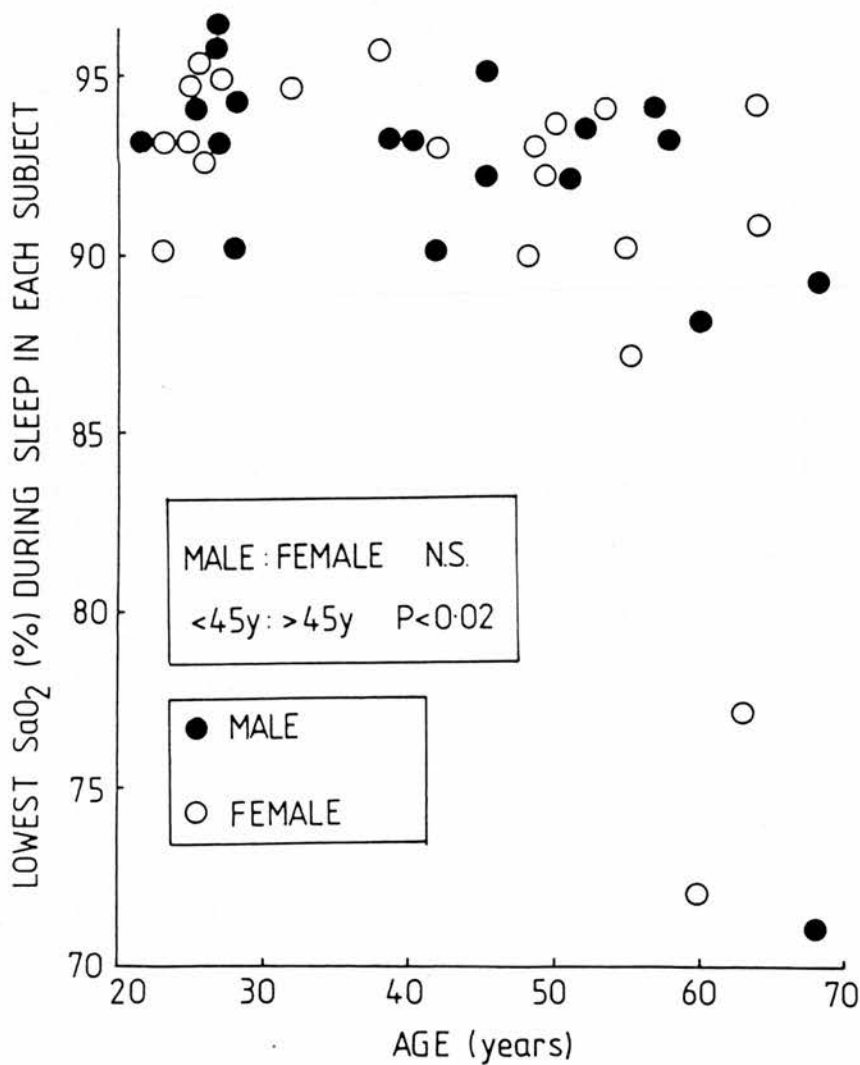


Fig 7 Lowest arterial oxygen saturation (SaO<sub>2</sub>) during sleep in relation to each subject's age and sex, showing that older subjects become more hypoxaemic than younger subjects, but that there is no sex difference at any age.

45 yr were also more hypoxaemic when awake than the younger subjects ( $p < 0.05$ ; table 3).

#### Sleep stage and breathing pattern during hypoxaemic episodes

Of the 28 hypoxaemic episodes, all but 2 were associated with apnoea or hypopnoea (appendix, tables 15, 16). Seventeen occurred during REM sleep, 10 in stage 2 sleep, and 1 in stage 1 sleep (appendix, tables 15, 16). The distribution of the hypoxaemic episodes through the different sleep stages was similar in both sexes (appendix, tables 15, 16).

#### Patient follow-up

In an attempt to determine the clinical significance of irregular breathing and hypoxaemia during sleep, I reviewed all the subjects who had more than 30 episodes of apnoea and/or hypopnoea per night, and/or or falls in  $\text{SaO}_2$  below 90%. The mean follow-up period was 71 (range 29 to 81) months after the sleep study was performed. These 7 subjects (4 M, 3 F) were 51 to 68 yr of age when studied. One later died at the age of 71 of a daytime myocardial infarction, approximately 3 years after the sleep study. The other 6 subjects were still alive at the time of writing. One of the women (63 yr old at the time of the study) had developed mild angina and tinnitus during the intervening 7 years but all the other patients had remained asymptomatic. Specifically, none of the 6 patients still available for review described any daytime somnolence, sleep disturbance, or cardiac failure.



## DISCUSSION

The above results show that even in non-obese healthy subjects breathing patterns and oxygenation during sleep show a wide variability. There was no sex difference in hypoxaemia or irregular breathing during sleep in this study, but the older subjects became more hypoxaemic and had more episodes of apnoea and hypopnoea than did the younger subjects. Some of the older subjects had more than 30 apnoeas per night (and thus satisfied the currently accepted criteria for a sleep apnoea syndrome) but there was no evidence that this was associated with increased morbidity or mortality over an average follow-up period of 6 years.

There was no sex difference in breathing and oxygenation during sleep in either the younger subjects or the older subjects. Thus these results are in agreement with previous (Block et al, 1980; Ancoli-Israel et al, 1981; Carskaddon and Dement, 1981) and concurrent (Kreiger et al, 1983; Ancoli-Israel et al, 1985; Bixler et al, 1985) studies which showed no sex difference in respiration during sleep in the elderly, but they contrast sharply with the observations of Block and colleagues (1979), who found a strong male predominance in irregular breathing and hypoxaemia during sleep. However, in that study by Block and colleagues the men were more hypoxic than the women when awake, and they were also both older and heavier than the women. Since each one of these factors would have tended to predispose the men to hypoxaemia and/or irregular breathing (see Chapter 4), they may account for the differences between the sexes

observed in that study. In the present study, the level of oxygenation when awake was similar in the two sexes, the men and women were age-matched, and none of the subjects was obese.

In the study by Block and colleagues (1979), the method of analysis was slightly different from ours, as their definition of hypopnoea required concomitant desaturation. This also would have tended to produce a sex differential in their results, as the men in that study started the night on a steeper part of the oxyhaemoglobin dissociation curve than the women. To make the results of the present study more strictly comparable to those of Block and colleagues, we analysed the present study using their definition, but the conclusion that there was no sex difference at any age was not altered.

Krieger and colleagues (1983b) recently made observations similar to our own in 40 normal subjects, aged 20 - 76 yr. Although their definitions of hypopnoea and apnoea differed from the conventional ones (being based on periods of 8 seconds rather than the conventional 10 seconds), they also observed no sex difference in breathing patterns during sleep. Measurements of oxygenation were not included in that study.

Most patients with the sleep apnoea syndrome are male, and many are obese (Guilleminault et al, 1978; Sullivan and Issa, 1985). The present study does not exclude a sex difference in sleep-disordered breathing in obese subjects (Harman et al, 1981). Harman and co-

workers (1981) found that asymptomatic obese men became hypoxaemic during sleep and that asymptomatic obese women did not. Again, unfortunately, the men in that study were considerably more hypoxic than the women when awake, and this could account for most of their excess sleep-disordered breathing. Further, some of the asymptomatic obese young women studied by Kopelman and colleagues (1983) did desaturate during sleep. Thus, it is not clear whether there is a sex difference in sleep-disordered breathing in obese subjects.

It has previously been reported that postmenopausal women have more irregular breathing and hypoxaemia during sleep than premenopausal women (Block et al, 1980), and this has led to speculation that progesterone, a ventilatory stimulant, may influence breathing patterns during sleep in normal subjects (Block et al, 1979,1980). In the present study we found that the increase in sleep-disordered breathing with age occurred equally in both sexes. Further, Douglas and colleagues (1982a) also failed to detect any sex difference in spontaneous ventilation during sleep in normal young subjects. Thus, physiological levels of circulating progesterone may have little influence on breathing during sleep, except perhaps in pregnancy (Brownwell et al, 1986).

Although many previous (Webb, 1974; Lafont et al, 1978; Block et al, 1979 and 1980; Carskaddon and Dement, 1981; Ancoli-Israel et al, 1981) and concurrent (Smallwood et al, 1983; Krieger et al, 1983; Bixler et al, 1985) studies have shown irregular breathing during

sleep to be common in the elderly, there is much less published data on oxygenation during sleep in normal subjects of different ages (Block et al, 1979 and 1980). The tendency for nocturnal hypoxaemia to increase with age in the present study was due to a combination of two factors. The older subjects had more apnoeas and hypopnoeas than the younger subjects, and also they were predisposed to falls in arterial oxygen saturation by having lower oxygen saturations when awake (Catterall et al, 1983; Stradling and Lane, 1983). The importance of sleep apnoea as a cause of nocturnal hypoxaemia in the elderly was recently noted by Bixler and colleagues (1985) although they did not assess the amount of hypopnoea during sleep in their elderly subjects. In the present study nocturnal hypoxaemia was associated with hypopnoea as well as apnoea.

During an average follow-up period of 6 years only 1 of our subjects with sleep-disordered breathing died. Furthermore, he was a 71 yr old man and died in the afternoon of a myocardial infarction, a condition extremely common in men of that age in this country. These results suggest that irregular breathing and hypoxaemia during sleep are relatively common in subjects over 50 yr of age but that the individuals affected are often asymptomatic and that their sleep-disordered breathing may be of little clinical significance. However, these data are based on relatively few subjects. There is a need for larger scale longitudinal studies of patients with asymptomatic sleep disordered breathing to determine its clinical significance.

The results of this study illustrate the limitations of the currently accepted criteria for diagnosis of the sleep apnoea syndrome. Block and colleagues (1979) were the first to question the usefulness of an arbitrary cut-off of 30 apnoeas per night (or 4 apnoeas per hour of sleep), mainly as a result of their observations on asymptomatic obese men. The present study, and also that of Krieger and colleagues (1983b), confirm that even non-obese healthy subjects can have more than 30 apnoeas per night, although this has only been reported in non-obese healthy subjects over the age of 50 yr. In fact there is probably no need to have such a low cut-off for diagnosis of the sleep apnoea syndrome since patients with this syndrome nearly always have many more apnoeas per night than 30 (Guilleminault et al, 1978).

Should hypopnoeas be included in the criteria for diagnosis of a sleep "apnoea" syndrome? The present study does not address this issue. However, it does show that nocturnal hypoxaemia in normal subjects is more often caused by hypopnoea than apnoea. There is very little data on the clinical significance of hypopnoea but we have recently described 5 patients with symptoms strongly suggestive of a sleep apnoea syndrome who had frequent hypopnoeas during sleep but relatively few apnoeas (Gould et al, 1986). This suggests that there may also be a "sleep hypopnoea syndrome", and that hypopnoeas, as well as apnoeas, during sleep should be included in the assessment of patients with a suspected sleep apnoea syndrome.

These results emphasise the importance of age-matched control

subjects in studies of breathing and oxygenation during sleep, and they also imply that sleep apnoea may sometimes be an incidental finding in patients over 50 yr of age. Hence, a sleep apnoea syndrome should be diagnosed only if the patient's symptoms suggest the diagnosis. Furthermore, even if a patient over the age of 50 yr is found to have frequent episodes of sleep apnoea, care must be taken to exclude other causes for his or her symptoms.

## SUMMARY - PART II

The purpose of the studies in this part of the thesis was to establish normal reference ranges for apnoea, hypopnoea and oxygenation during sleep, and to investigate the effects of age and sex on these variables.

Ear oxygen saturation ( $\text{SaO}_2$ ), oronasal airflow, chest movement and electroencephalographic sleep stage were monitored throughout an undisturbed night's sleep in 40 non-obese healthy adults (19 men and 21 women), aged 21 - 68 yr.

The results were as follows:

1. There was a wide range of irregular breathing and oxygenation during sleep in the normal subjects, especially in those over the age of 50 yr.
2. Older subjects had more irregular breathing and hypoxaemia during sleep than young subjects.
3. In these non-obese healthy adults, irregular breathing and hypoxaemia during sleep were equally common in men and women at all ages.
4. Hypoxaemia during sleep was associated with hypopnoea as well as apnoea.

5. Seven subjects had more than 30 episodes of apnoea and/or hypopnoea per night, an/or  $\text{SaO}_2$  falls below 90%, but none of these individuals developed symptoms of the sleep apnoea syndrome over an average follow-up period of six years.

The following conclusions were drawn:

1. Studies of breathing and oxygenation during sleep should include age-matched control subjects.
2. Full assessment of irregular breathing during sleep should include an assessment of the amount of hypopnoea as well as the number of apnoeas.
3. There is no fundamental sex difference in irregular breathing and oxygenation during sleep. Previous reports to the contrary can probably be explained by poor matching of the men and women with respect to age and sex.
4. In asymptomatic subjects over the age of 50 yr, irregular breathing and hypoxaemia during sleep may be of little clinical significance. However, this conclusion is based on observations of only a small number of subjects, and long-term studies involving more subjects will be needed to confirm this.



5. The current definition of the sleep apnoea syndrome should be modified. In particular, the syndrome should not be diagnosed from the number of apnoeas (and hypopnoeas) alone; diagnosis should also include consideration of the patient's symptoms.

### **Part III**

#### **BREATHING AND OXYGENATION DURING SLEEP IN ASTHMA**

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## Chapter 5

### REVIEW OF THE LITERATURE

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Despite the clinical importance of nocturnal asthma (see Chapter 1) there have been relatively few studies of the physiological changes which occur during sleep in asthmatic patients. However, there is abundant evidence that sleep can induce changes in respiration in other conditions.

In this chapter I shall review (i) evidence that disordered breathing induced by sleep can be clinically significant, (ii) previous studies of oxygenation during sleep in patients with respiratory disease, and (iii) previous studies of EEG sleep stages in patients with asthma.

#### 1. Irregular breathing during sleep

##### 1(i) The sleep apnoea syndrome

In 1965, Gastaut and colleagues observed frequent episodes of apnoea during sleep in the Pickwickian syndrome (Burwell et al, 1956). Although this was not the first description of sleep apnoea - Broadbent having clearly described apnoea during deep sleep in a

healthy elderly man in 1877 - the patients described by Gastaut and colleagues were remarkable in that they had very large numbers of apnoeas and, as a result (Drachman and Gumnit, 1962), frequent disruptions of sleep. The authors suggested that the episodes of sleep apnoea might be the underlying cause of the daytime hypersomnolence which occurs in the Pickwickian syndrome.

The fact that these patients actually had apnoea during sleep was not judged to be particularly remarkable, however, since patients with the Pickwickian syndrome hypoventilate even when awake (Burwell et al, 1956). Furthermore, sleep apnoea was subsequently observed in other conditions associated with hypoventilation when awake, including Ondine's curse (primary alveolar hypoventilation; Lugaresi, 1968), bilateral cervical cordotomy and other neurosurgical lesions (Fielding, 1975; Krieger, 1978; Vella et al, 1984), poliomyelitis (Hill et al, 1983) and encephalitis (White et al, 1983).

In 1973, Guilleminault and colleagues reported recurrent episodes of sleep apnoea in two patients who had presented with insomnia. Importantly, these patients did not have ventilatory failure when awake. Guilleminault and colleagues suggested that sleep apnoea might be the primary cause of these patients' symptoms and named the new syndrome "Insomnia with sleep apnoea" (Guilleminault et al, 1973). They subsequently observed sleep apnoea in many more patients presenting to a sleep disorders clinic, and noted that insomnia was less common than a variety of other symptoms, including daytime hypersomnolence, loud snoring, and morning headaches

(Guilleminault et al, 1976 and 1978). They coined the term "sleep apnoea syndrome" (Guilleminault et al, 1976, 1978, 1980, 1984), and their observations were confirmed by many other workers (Lugaresi et al, 1978; Remmers et al, 1978; Orr et al, 1979; Sullivan et al, 1981; Coleman et al, 1982). The episodes of apnoea in most patients were shown to result from intermittent collapse of the upper airway during sleep (Remmers et al, 1978; Onal et al, 1982), often in patients who had anatomical narrowing of the pharynx while awake (Harponi et al, 1983; Rivlin et al, 1984), and recent studies by Sullivan and colleagues (1981) have shown that the condition can be treated effectively by preventing upper airway collapse, using continuous positive airways pressure administered via the nose. The prevalence of the sleep apnoea syndrome is uncertain (Shapiro et al, 1982; Ancoli-Israel et al, 1985; McNicholas, 1986) but one recent study of working men in Israel suggested that the condition may affect some 1% of the adult male population (Lavie et al, 1983).

The discovery of the sleep apnoea syndrome established the clinical importance of disordered breathing during sleep, and led to the widespread application of sleep studies in clinical practice (Kryger, 1985; Martin et al, 1985). Studies of breathing patterns during sleep are relatively new to clinical medicine, however, and the extent of their usefulness has still to be defined. Some of the issues that need to be clarified are discussed below. The sleep apnoea syndrome itself will not be discussed in detail in this thesis, as it has been the subject of many recent reviews (Guilleminault et al, 1976, 1978, 1980, 1984; Cherniak, 1981; White,

1985; Sullivan and Issa, 1985).

1(ii) Sleep apnoea in other conditions

Sleep apnoea has been implicated in some cases of the sudden infant death syndrome (SIDS; Kelly, 1983, Guilleminault et al, 1986). However, an increased risk for SIDS does not apply equally to all infants with apnoea (Kelly and Shannon, 1982; Southall et al, 1982) and the majority of SIDS victims have not previously been identified as having had apnoea (Mandell, 1981). The relationship between SIDS and sleep apnoea is still unclear, therefore.

In adults, an increased prevalence of sleep apnoea has recently been noted in patients with essential hypertension (Kales et al, 1984; Lavie et al, 1984; Fletcher et al, 1985). Since episodes of sleep apnoea are associated with a rise in systemic blood pressure (Coccagna et al, 1972; Schroeder et al, 1978) and since 60-80% of patients with severe sleep apnoea are hypertensive (Guilleminault et al, 1980b and 1981), it has been suggested (Kales et al, 1984; Fletcher et al, 1985) that sleep apnoea may be a cause of hypertension. This intriguing relationship between sleep apnoea and hypertension clearly warrants further study.

Guilleminault and colleagues (1980a) reported an increased number of apnoeas during sleep in patients with chronic obstructive airways disease. However, their patients had presented to a sleep disorders clinic, and subsequent studies (Catterall et al, 1983) showed no increase in sleep apnoea in patients with chronic bronchitis and

emphysema who had presented to a clinic for respiratory diseases. These results, and also more recent observations by Goldstein and colleagues (1984), suggest that chronic bronchitis and emphysema is not usually associated with an increased number of sleep apnoeas, but that the sleep apnoea syndrome can occasionally coexist with chronic obstructive airways disease.

#### **1(iii) Sleep hypopnoea**

As well as complete apnoea during sleep, hypopnoea can occur, as discussed in Sections I and II. Episodes of sleep hypopnoea usually occur during REM sleep, and in patients with pre-existing hypoxaemia they can cause marked arterial oxygen desaturation (Flick and Block, 1977; Douglas et al, 1979; Catterall et al, 1983a). Recent studies suggest that there may also be a "sleep hypopnoea syndrome" (Gould et al, 1986; see Chapter 4).

#### **1(iv) Breathing patterns during sleep in asthma**

It is clear from the above examples that irregular breathing during sleep has been implicated in the pathogenesis of a variety of conditions. Asthmatic patients have marked worsening of symptoms at night, but it is not known whether they have an increased number of apnoeas or hypopnoeas during sleep, nor is it known whether asthmatics have prolonged expiration during episodes of nocturnal bronchoconstriction, as frequently observed clinically during acute exacerbations of asthma (Batten, 1978; Fraser and Parre, 1979). If a characteristic breathing pattern were associated with nocturnal bronchoconstriction, it would facilitate the study of nocturnal

asthma, for there is currently no satisfactory method of measuring airway calibre while patients are asleep (see Chapter 2).

## **2. Oxygenation during sleep in patients with respiratory disease**

Non-invasive techniques for studying oxygenation and breathing during sleep have been used not only to identify patients with the sleep apnoea syndrome - in whom the major abnormalities usually lie not in the lungs but in the upper airways or in the central control of ventilation (Turino and Goldring, 1978) - but also to study patients with respiratory disease. Most of these studies have been performed in patients with chronic bronchitis and emphysema.

### **2(i) Nocturnal hypoxaemia in chronic bronchitis and emphysema**

Marked falls in arterial oxygen saturation during sleep are now known to be common in patients with chronic airflow limitation. This was first demonstrated by Trask and Cree (1962), who measured arterial oxygen saturation continuously during sleep in 7 emphysematous patients, using a Water's ear oximeter. They found that all 7 patients had worsening of hypoxaemia during sleep, and they also noted that the lowest saturations during sleep were recorded in those whose saturations were lowest when awake. They did not confirm sleep electroencephalographically (see Chapter 2), however, the first study to do so being that of Pierce and colleagues (1966). These investigators, and subsequently others (Atlan et al, 1968; Interiano et al, 1972; Leitch et al, 1976), sampled arterial blood intermittently during the night in patients with chronic obstructive



airways disease and found that the mean fall in arterial oxygen tension during sleep ranged from 4 mmHg (Atlan et al, 1968) to 7 mmHg (Pierce et al, 1966).

Koo, Sax and Snider (1975) extended these observations by showing that the arterial oxygen tension was lower in REM sleep than in NREM sleep. However, their observations were also made from intermittent samples of arterial blood.

The episodic nature of nocturnal hypoxaemia in these patients was demonstrated conclusively by Flick and Block (1977) who made continuous measurements of arterial oxygen saturation, using a Hewlett-Packard ear oximeter (Saunders et al, 1976; Douglas et al, 1979b; see Chapter 2). In 10 patients with severe chronic obstructive airways disease they observed transient falls in arterial oxygen saturation of 12 - 44% from the baseline during sleep, with lowest absolute  $\text{SaO}_2$  levels averaging 68%. These observations were confirmed and extended by Douglas and colleagues (1979a) who studied oxygenation during sleep in 12 patients with severe chronic bronchitis and emphysema, of whom 10 were "blue bloaters" (Dornhorst, 1955) and 2 "pink puffers". All 10 of the "blue bloaters" had episodes of transient hypoxaemia in which arterial oxygen saturation fell by more than 10%, and the great majority (23/28) of the hypoxaemic episodes occurred in REM sleep. The "pink puffers", in contrast, despite equally severe airflow limitation, had no 10% falls in oxygen saturation. It was suggested (Flick and Block, 1977; Flenley, 1978; Douglas et al, 1979a) that these recurrent episodes of

nocturnal hypoxaemia might lead to cor pulmonale and secondary polycythaemia, a hypothesis supported by the observation that pulmonary arterial pressure rises during the hypoxaemic episodes (Coccagna and Lugaresi, 1978; Douglas et al, 1979a; Boysen et al, 1979; Fletcher and Levin, 1984; Catterall et al, 1985; Connaughton et al, 1985) and by recent studies in rats, in which repetitive transient hypoxaemia of similar magnitude increased both right ventricular weight and red cell mass (Moore-Gillon and Cameron, 1985).

The mechanism of transient nocturnal hypoxaemia in chronic bronchitis and emphysema has been studied by a number of authors. We and others have shown that most of the hypoxaemic episodes are associated not with apnoea, but with hypoventilation (Wynne et al, 1979; Fleetham et al, 1980; Skatrud et al, 1981; Catterall et al, 1983; Fletcher et al, 1983). However, there is debate whether the hypoxaemic episodes are due only to hypoventilation since the fall in arterial oxygen tension during the episodes is consistently greater than the rise in arterial carbon dioxide tension. Some authors (Pierce et al, 1966; Koo, Sax and Snider, 1975; Leitch et al, 1976; Flick and Block, 1977; Fletcher et al, 1983) have argued that worsening of ventilation/perfusion balance must also be invoked to explain the observed changes in arterial gas tensions, but others (Douglas et al, 1982d; Catterall et al, 1983 and 1985) have argued that they are compatible with hypoventilation alone, since the conditions during REM sleep are non steady-state. In order to clarify this point, we recently designed a simple model of nocturnal

hypoxaemia (Catterall et al, 1985). Four normal awake subjects simulated the breathing pattern observed during the hypoxaemic episodes of REM sleep while breathing a hypoxic gas mixture, and arterial blood was sampled from an indwelling catheter at 90 second intervals. We found that the changes in arterial gas tensions were similar to those observed during the actual nocturnal hypoxaemic episodes. These results suggest that it is unnecessary to invoke changes in ventilation/perfusion balance to explain transient nocturnal hypoxaemic episodes in patients with chronic bronchitis and emphysema, although they do not exclude such changes (Fletcher et al, 1983).

#### **2(ii) Nocturnal hypoxaemia in other respiratory disorders**

Episodes of hypoxaemia during sleep have also been described in kyphoscoliosis (Mezon et al, 1980; Guilleminault et al, 1981), diaphragmatic paralysis (Skatrud et al, 1980), cystic fibrosis (Muller et al, 1980; Tepper et al, 1983) and interstitial lung disease (Bye et al, 1984; Perez-Padilla et al, 1985). However, there is little data on the effects of nocturnal asthma on gas exchange.

#### **2(iii) Nocturnal oxygenation in asthma**

Hetzel and colleagues (1977b) measured arterial gas tensions at 6 am and 2 pm in 7 asthmatic patients who were convalescing after an acute attack of asthma and who had morning dips in PEFV of more than 25% of their highest daily readings. At both times of day, alveolar arterial oxygen tension gradient was widened and arterial oxygen

tension correspondingly low. Arterial oxygen tension rose by an average of 0.5 kPa between 6 am and 2 pm, with an average fall in arterial carbon dioxide tension of 0.1 kPa, but neither of these changes was statistically significant.

At the time that the studies in this thesis were first reported, there had been no continuous measurements of oxygenation during the night in patients with asthma.

### **3. Sleep in patients with asthma**

Disturbed sleep is a common complaint in patients whose asthma is poorly controlled. However, there is evidence that even relatively mild asthmatics have disturbed sleep, as judged electroencephalographically. Kales and colleagues (1968) compared the electroencephalographic sleep patterns of 6 young adult asthmatics with those of age-matched control subjects who had previously been studied in the same laboratory. The patients selected were having nocturnal symptoms but they were all out-patients and they "were not so disabled that they were not sleeping or working". The asthmatics had more frequent awakenings than the control subjects, with a significant reduction in both stage 4 sleep and total sleep time. A similar disruption of sleep pattern compared to age-matched control subjects was observed in 10 asthmatic children, of whom 6 were out-patients and 4 were in a hospital for asthmatic children (Kales et al, 1970).

However, these studies did not distinguish the effects of asthma

itself from the effects of the patients' medication, since all of these patients were regular users of either oral ephedrine, aminophylline or oral phenobarbital, each of which can affect the central nervous system and thus probably alter sleep patterns (Rall, 1980; Weiner, 1980; Rhind et al, 1985). The patients were asked to omit their usual night-time medication but this would not have removed their effect totally since, on the one hand, the sudden withdrawal of drugs that affect sleep can itself affect sleep patterns (Jaffe, 1980), whilst on the other hand phenobarbital has a long half-life (mean 86 hours in adults; Alvin et al, 1975) and may therefore still have been present in effective concentrations on at least some of the study nights. Since ephedrine and phenobarbital are rarely used to treat asthma nowadays, the current relevance of these results is uncertain.

In summary, nocturnal oxygenation and breathing patterns have not been studied in asthma. Electroencephalographic sleep patterns have been recorded, but most of the data has been collected from children and the relevance of that data to current practice is uncertain for the patients were receiving drugs that are now rarely used to treat asthma.

The next three chapters contain the results of studies of breathing patterns, oxygenation and electroencephalographic sleep stages at night in patients with asthma. The investigation described in chapter 6 involved the study of 20 patients with relatively stable

asthma throughout a night's sleep. Their electroencephalographic sleep patterns, breathing patterns and arterial oxygen saturation were compared with those of 34 age-matched normal subjects (chapter 4) and those of 20 patients with severe chronic bronchitis and emphysema.

Chapter 7 contains an account of similar studies in a patient with persistent daytime hypoxaemia due to asthma. I wished to know whether this patient had more severe nocturnal hypoxaemia than other asthmatic patients.

The study described in chapter 8 was designed to determine the effect of ketotifen on oxygenation, breathing patterns and sleep patterns in asthma. Ketotifen is a relatively new drug for the treatment of asthma, but it also causes drowsiness. Since sleep is associated with hypoxaemia in patients with chronic airflow limitation, I was concerned that ketotifen might aggravate nocturnal hypoxaemia in patients with asthma.

## Chapter 6

### BREATHING AND OXYGENATION DURING SLEEP IN PATIENTS WITH CHRONIC STABLE ASTHMA

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In this study, arterial oxygen saturation, breathing patterns and EEG sleep stage were monitored throughout the night in 20 patients with asthma. The results were compared with those of similar studies in:

- (a) The 34 healthy subjects described in Section I who were of similar age to the asthmatic patients.
- (b) 20 patients with chronic bronchitis and emphysema. The studies of these bronchitic patients were initiated by Dr N J Douglas (Douglas et al, 1979a) and completed by me (Catterall et al, 1983a, 1985).

### METHOD

#### Patients

The patients with asthma (15 men, 5 women) were aged 18 - 59 (mean 36.9) yr (table 4). They were recruited from the asthma clinics of the Royal Infirmary and City Hospital, Edinburgh independent of any symptoms of nocturnal asthma. All had reversible airways

TABLE 4

## CLINICAL DETAILS OF ASTHMATIC PATIENTS STUDIED IN SECTION III

Subject No	Age (yr)	Sex	FEV <sub>1</sub> (l)		Skin Tests	FH of atopy	Smoker	Regular treatment
			Highest	Lowest				
1	18	M	2.4	4.2	Pos	Yes	Yes	S
2	18	M	1.3	4.3	Pos	No	No	S,B
3	21	M	2.3	3.5	Pos	No	Yes	S,B
4	21	M	2.6	4.1	Pos	Yes	No	S,B
5	22	M	0.7	3.8	Pos	Yes	No	S,P
6	23	F	1.2	3.0	Pos	No	No	S,B
7	27	M	0.5	2.8	Pos	No	Yes	S,B,P
8	30	F	1.0	1.7	Pos	Yes	No	S,I,P
9	34	F	2.3	3.7	Neg	No	No	S,B
10	34	M	1.5	4.4	Neg	Yes	No	S,B
11	37	M	0.9	1.9	Pos	Yes	Ex	S,B,P
12	39	F	1.0	2.0	Pos	No	No	S,B,P
13	40	M	1.5	2.9	Neg	Yes	Yes	S,B,T
14	50	M	1.2	2.5	Pos	Yes	Ex	S,B,O
15	50	M	1.0	2.7	Pos	No	Ex	S,C
16	51	F	0.6	1.9	Pos	Yes	Ex	S,B,C,I,O
17	53	M	0.5	2.7	Pos	Yes	Ex	S,B
18	56	M	0.9	2.0	Neg	No	No	S,B
19	56	M	1.2	2.6	Neg	No	Ex	S,B
20	59	M	0.5	1.3	Pos	No	No	S,I,B,P

M, male; F, female; Lowest and highest FEV<sub>1</sub> recorded at clinical during preceding 1-2 years; Pos, positive skin prick tests to at least 2 common allergens; Neg, negative skin prick tests; FH, family history; S, inhaled beta-2 agonist; B, inhaled corticosteroid; I, inhaled ipratropium; C, inhaled disodium cromoglycate; P, oral prednisolone. 5-10 mg daily, T, oral theophylline; O, oral beta-2 agonist.



obstruction with a documented increase in  $FEV_1$  of more than 20% after inhalation of bronchodilators. Fifteen had positive skin prick tests to *Dermatophagoides pteronyssinus* and/or grass pollens (Bencard, Brentford, Middlesex) and 10 had a family history of atopy.

The patients were in a stable state with a mean diurnal variation in PEF (measured four times daily for 3 days before and 3 days after the study in 13 patients) not exceeding 30% (mean 14%) of the highest daily value, and none had had an acute attack of asthma in the previous 6 weeks. Fifteen had a history of nocturnal wheeze, 6 were regular users of oral prednisolone (5 or 10 mg daily), 16 took inhaled corticosteroids regularly, and 2 used inhaled disodium cromoglycate regularly (table 4). These were discontinued during the study, each at an unchanged dose, but oral theophyllines (regularly taken by 1 patient) and oral beta sympathomimetic agents (2 patients) were withdrawn 24 hours before the study. Inhaled beta sympathomimetic agents (used by all patients) and ipratropium bromide (3 patients) were each withheld for 6 hours before the study.

The age-matched control subjects were the 34 subjects described in Section I who were under 60 yr of age (table 2). Their mean age was 38.5 yr (range 18-58 yr).

The 20 patients with chronic bronchitis (Medical Research Council, 1965) and emphysema all had severe irreversible airways obstruction ( $FEV_1 < 1$  litre) and none had had an acute exacerbation of their disease for at least 6 weeks prior to being studied. Thirteen of

the patients fulfilled our criteria for being "blue and bloated" [type B (Burrows et al, 1964), non-fighters (Robin and O'Neill, 1963)], having daytime arterial hypoxaemia ( $\text{PaO}_2 < 8 \text{ kPa}$ ) and hypercapnia ( $\text{PaCO}_2 > 6 \text{ kPa}$ ), pulmonary hypertension (mean pulmonary arterial pressure  $> 18 \text{ mmHg}$ ) and secondary polycythaemia (red cell mass  $> 28 \text{ ml/kg}$ ). Seven patients were termed "pink and puffing" (type A, fighters), having relatively mild arterial hypoxaemia ( $\text{PaO}_2 > 8 \text{ kPa}$ ) and a normal  $\text{PaCO}_2$  ( $< 6 \text{ kPa}$ ) when awake. Both the "blue bloaters" (mean age 58.4 yr) and the "pink puffers" (mean age 63.6 yr) were older than the asthmatic patients (table 5).

#### Recording and analysis of EEG sleep stage, breathing patterns and arterial oxygen saturation

The patients slept in a quiet darkened room on two consecutive nights, with the first night for acclimatisation. Electroencephalographic sleep stage, breathing patterns and arterial oxygen saturation were recorded and analysed by the methods described in Section II.

#### Breath-by-breath analysis of breathing patterns

In 12 subjects (6 asthmatic patients and 6 control subjects), the magnetometer signal was analysed on-line throughout the night by a PDP 11/23+ computer (Digital Equipment Corporation, Maynard, MA, USA) which had been programmed to measure the following variables for each breath:

Expiratory time ( $T_e$ )

Inspiratory time ( $T_i$ )

Breath period ( $T_{\text{tot}} = T_i + T_e$ )

Respiratory duty cycle ( $T_i/T_{\text{tot}}$ )

Amplitude of chest movement, this being a semi-quantitative measure (see Chapter 2) of tidal volume (" $V_t$ ")

"Inspiratory flow rate" (" $V_t$ "/ $T_i$ )

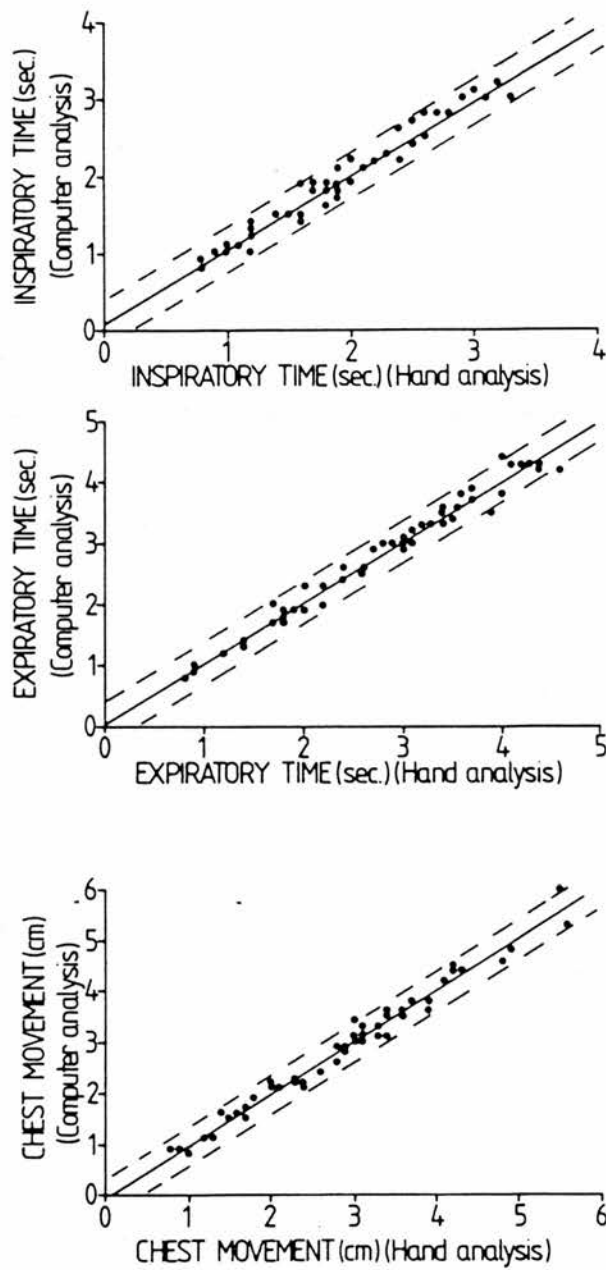
"Minute ventilation" (" $V_t/T_{\text{tot}}$ ")

Arterial oxygen saturation ( $\text{SaO}_2$ )

The computer was programmed for this analysis by Dr P K Wraith (Department of Respiratory Medicine, University of Edinburgh), with my assistance. The computer analysis was compared with hand analysis in one normal subject when awake over 50 breaths during which the breathing pattern was varied. For each of the independent variables measured ( $T_i$ ,  $T_e$  and " $V_t$ ") the slope of the relationship between the values obtained by computer analysis and the values obtained by hand analysis was within 4% of unity, with a correlation coefficient  $> 0.98$  (fig 8).

Artefacts due to body movement were excluded by hand analysis of the magnetometer signal record. Some body movements were also associated with an obvious change in the calibration of the magnetometer, a change which persisted after the actual movement. This limited the interpretation of changes in "tidal volume" during the night, as explained below.

To compare the effects of (i) time of night and (ii) REM sleep (both of which may be associated with significant bronchoconstriction in



**Fig 8** Comparison between measurements obtained by hand analysis and measurements obtained by computer analysis for inspiratory time, expiratory time and amplitude of chest movement for each breath during 50 breaths in 1 normal subject.

asthmatic patients; see Chapter 11) on these breath-by-breath measurements, the following periods were selected for analysis:

1. Breathing during the first 10-15 minute period of uninterrupted NREM sleep after 1 am was compared with breathing during the first 10-15 minute period of uninterrupted NREM sleep after 4 am. Since the calibration of the magnetometer sometimes varied during the night (due to body movement), it was not possible to compare "tidal volumes" at these two times - only respiratory timing could be compared.
2. Breathing during 10-15 minutes of uninterrupted REM sleep was compared with breathing during an immediately preceding 10-15 minute period of uninterrupted NREM sleep, irrespective of the time of night. Sections were chosen for analysis only if they contained no obvious change in the calibration of the magnetometer (recognised by a sudden change in the amplitude of the signal following body movement) throughout the 20-30 minute period, a criterion that was met in 5 asthmatics and 5 control subjects. Thus, in this analysis, it was possible to assess changes in "tidal volume".

#### Calculation of arterial oxygen tensions

The ear oximeter measures arterial oxygen saturation. Arterial oxygen tensions were calculated (Severinghaus, 1966) from the arterial oxygen saturation when awake and from the lowest saturation during sleep, assuming:

- (i) a similar oxyhaemoglobin dissociation curve in all subjects

- (ii) an arterial hydrogen ion concentration,  $[H^+]$  of 40 nmol/l
- (iii) a body temperature of 37°C

Errors due to the first assumption are probably small (Tweeddale et al, 1976 and 1977). The second and third assumptions are also unlikely to be associated with large errors, since arterial hydrogen ion concentrations rise during sleep whereas temperature falls at night and these changes have opposite effects on the oxyhaemoglobin dissociation curve. Measurements of arterial hydrogen ion concentration during sleep have not been made in asthmatic patients, but in patients with chronic bronchitis and emphysema the mean values recorded in three studies (Koo et al, 1975; Leitch et al, 1976; Douglas et al, 1979a) averaged 49 nmol/l. Kreider and colleagues (1958) found the mean lowest temperature at night to be 36.2°C. If these values of  $[H^+]$  (49 nmol/l) and temperature (36.2°C) are used to calculate  $PaO_2$  from, say, the lowest  $SaO_2$  during sleep in the asthmatic patients (mean 85.5%), the resulting  $PaO_2$  would be 7.1 kPa, compared with a  $PaO_2$  of 6.7 kPa if  $[H^+]$  is assumed to be 40 nmol/l and temperature 37°C, i.e. the error of these two assumptions in this example would be 6%.

The largest source of error in this method of determining arterial oxygen tension lies in the measurement of arterial oxygen saturation by the ear oximeter, particularly at the higher levels of  $SaO_2$ . In non-smokers (ie when the carboxyhaemoglobin level is < 3%), the ear oximeter has an error of  $\pm 4\%$  (Douglas et al, 1979b). At the highest level of  $SaO_2$  recorded in any asthmatic patient (98%), an error of

+4% in the oxygen saturation would mean an error of +66% in the calculated  $\text{PaO}_2$  ( $\text{PaO}_2$  corresponding to  $\text{SaO}_2$  of 98%, assuming  $[\text{H}^+]$  of 40 nmol/l and a temperature of  $37^\circ\text{C}$ , = 15.5 kPa;  $\text{PaO}_2$  corresponding to  $\text{SaO}_2$  of 94% = 9.3 kPa), whereas a +4% error at the lowest average  $\text{SaO}_2$  recorded during sleep in the asthmatic patients (mean 85.5%) would mean a +10% error in the calculated  $\text{PaO}_2$  ( $\text{PaO}_2$  corresponding to  $\text{SaO}_2$  of 85.5% = 6.7 kPa;  $\text{PaO}_2$  corresponding to  $\text{SaO}_2$  of 81.5% = 6.1 kPa). These are the worst possible errors that would be anticipated in an individual asthmatic patient, and in a group of patients the average error would almost certainly be much less.

Thus the transformation from arterial oxygen saturation to arterial oxygen tension is only an approximation. However, direct measurement of oxygen tension would have involved the insertion of an arterial catheter, a procedure that could not have been justified ethically in most of our subjects. Furthermore, it is very difficult to sample arterial blood at exactly the lowest oxygen saturation during sleep since it is impossible to predict exactly when this is going to occur. To estimate the maximal change in  $\text{PaO}_2$  during sleep, therefore, it was necessary to calculate oxygen tension from saturation.

## RESULTS

### 1. Requests to use inhalers during the night in the asthmatic patients

Five of the asthmatic patients asked to use a bronchodilator inhaler during the night - at 5.55 am (patient 2), 1.30 am (patient 8), 5.35 am (patient 10), 4.40 am (patient 14), and 5.15 am (patient 15). Three of these awakenings were from NREM sleep (two from stage 2 sleep and one after 10 minutes of stage 1 sleep following a period of stage 2 sleep) and one was from REM sleep. The other request to use an inhaler was made after 15 minutes of wakefulness. Thus there was no clear relationship between requests to use a bronchodilator inhaler and either the time of night or the EEG sleep stage. After using an inhaler each patient was allowed to return to sleep.

### 2. Overnight fall in FEV<sub>1</sub> in the asthmatic patients

All the asthmatic patients showed a fall in FEV<sub>1</sub> overnight. The FEV<sub>1</sub> before sleep averaged 2.3 l and the FEV<sub>1</sub> after sleep (taken as the level on waking during the night in the five patients who used a bronchodilator inhaler in the night, and as the level at "lights on" in the remaining patients) averaged 1.5 l ( $p < 0.001$ ; appendix, table 19). All of these measurements were made before the use of a bronchodilator inhaler. One patient had used an inhaler before a measurement was taken and his FEV<sub>1</sub> measurements were therefore excluded from the analysis.



### 3. Sleep

3(i) Asthmatics vs normal subjects: The asthmatic patients slept less well than the normal subjects (table 5, fig 9). Time in bed was similar in the two groups (table 5), but the asthmatics spent more of that time awake than did the normal subjects (table 5), with less time in stage 2 sleep ( $p < 0.001$ ), less time in slow wave sleep (stages 3 + 4;  $p < 0.02$ ) and less time in REM sleep ( $p < 0.01$ ) than the normal subjects (table 5). Total sleep time was on average 84 minutes less in the asthmatics than in the normal subjects ( $p < 0.001$ ; table 5).

When expressed as a percentage of each subjects' total sleep time, the durations of each sleep stage were similar in the asthmatics and normal subjects, with the exception of stage 1 sleep which occupied a significantly greater proportion of total sleep time (TST) in the asthmatics (mean 12.1% of TST) than in the normal subjects (mean 7.1% of TST;  $p < 0.02$ ).

### 3(ii) Asthmatics vs patients with chronic bronchitis and emphysema:

Despite their difference in age (Williams et al, 1974), the asthmatic patients and the "pink puffers" had a similar duration and quality of sleep (table 5; fig 9). Total sleep time in the asthmatic patients was significantly shorter than in the "blue bloaters" but there was no significant difference between the asthmatics and the "blue bloaters" in either the sleep efficiency index or the duration of any individual sleep stage (table 5; fig 9).

TABLE 5 (cont'd)

	ASTHMA (n=20)	NORMAL (n=34)	CHRONIC BRONCHITIS AND EMPHYSEMA	
			Pink puffers (n=7)	Blue bloaters (n=13)
	Mean ±SE	Mean ±SE	Mean ±SE	Mean ±SE
<b>Arterial oxygen saturation</b>				
SaO <sub>2</sub> awake (%)	95.4 <sup>+</sup> <sub>0.5</sub>	97.0 <sup>+</sup> <sub>0.2</sub> ****	94.0 <sup>+</sup> <sub>0.6</sub>	78.2 <sup>+</sup> <sub>3.0</sub> ****
Lowest SaO <sub>2</sub> asleep (%)	86.0 <sup>+</sup> <sub>1.1</sub>	92.8 <sup>+</sup> <sub>0.4</sub> ****	81.3 <sup>+</sup> <sub>2.6</sub>	52.4 <sup>+</sup> <sub>14.00</sub> ****
No. of hypoxaemic episodes	2.3 <sup>+</sup> <sub>0.5</sub>	0.4 <sup>+</sup> <sub>0.1</sub> ****	3.6 <sup>+</sup> <sub>0.9</sub>	> 50****
Maximal SaO <sub>2</sub> fall	9.4 <sup>+</sup> <sub>0.9</sub>	4.2 <sup>+</sup> <sub>0.7</sub> ****	12.9 <sup>+</sup> <sub>2.8</sub>	25.9 <sup>+</sup> <sub>2.5</sub> ****
Calculated PaO <sub>2</sub> fall (kPa)	3.6 <sup>+</sup> <sub>0.3</sub>	3.8 <sup>+</sup> <sub>0.3</sub>	3.2 <sup>+</sup> <sub>0.6</sub>	2.2 <sup>+</sup> <sub>0.8</sub> ***
% PaO <sub>2</sub> fall	43 <sup>+</sup> <sub>10</sub>	29 <sup>+</sup> <sub>2</sub>	33 <sup>+</sup> <sub>5</sub>	36 <sup>+</sup> <sub>3</sub>

Maximal SaO<sub>2</sub> fall = SaO<sub>2</sub> awake - lowest SaO<sub>2</sub> asleep.

Calculated PaO<sub>2</sub> fall = PaO<sub>2</sub> awake (calculated) - lowest PaO<sub>2</sub> asleep (calculated).

% PaO<sub>2</sub> fall = (Maximal PaO<sub>2</sub> fall/PaO<sub>2</sub> awake) x 100.

The number of hypoxaemic episodes (ie SaO<sub>2</sub> falls > 4%) in the "blue bloaters" was not counted accurately.

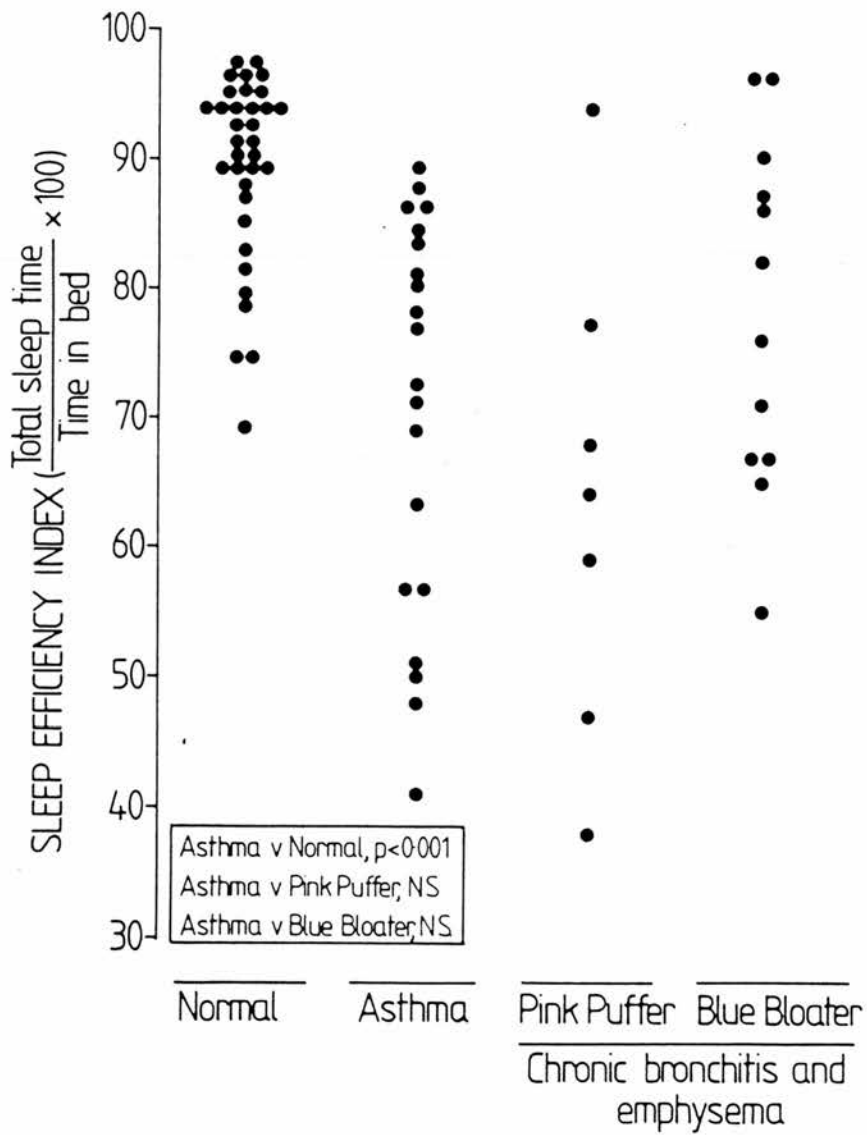
Results without asterisk were not significantly different from those in the asthmatics.

\* Different from asthma,  $p < 0.05$ .

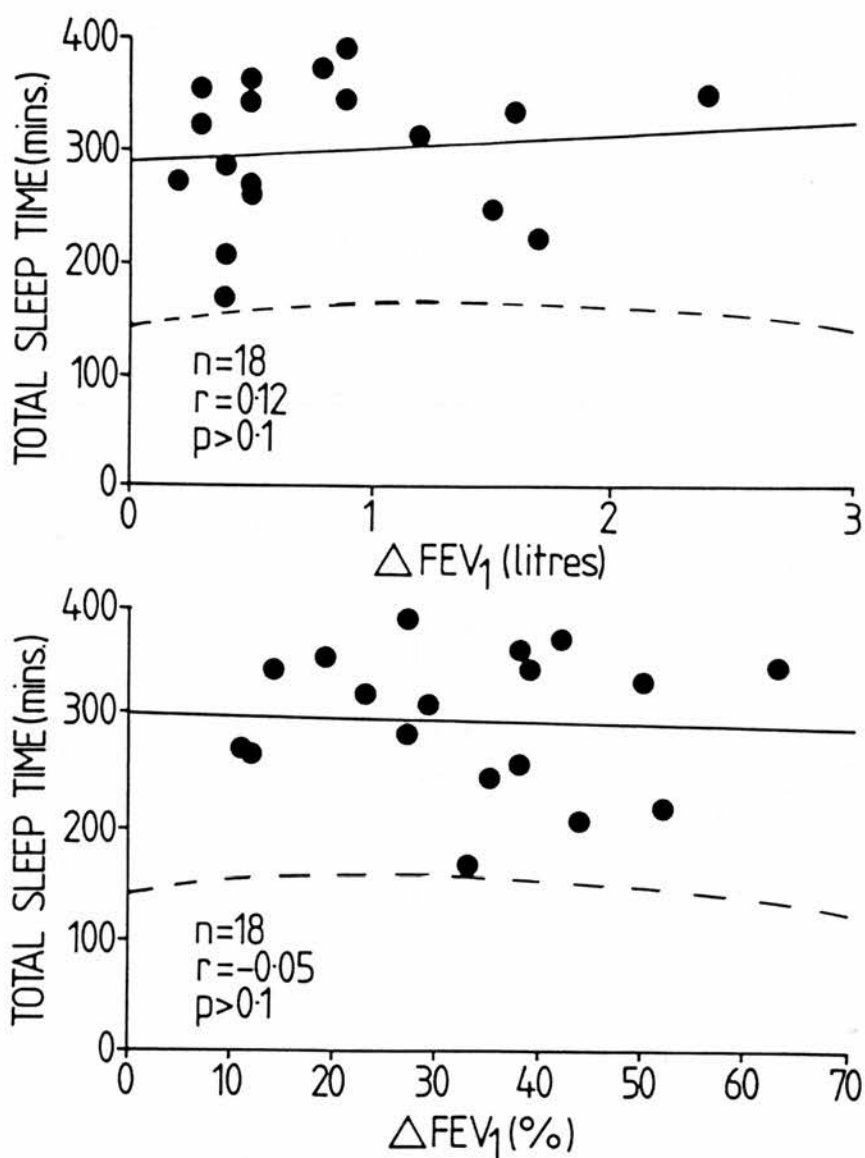
\*\* Different from asthma,  $p < 0.02$ .

\*\*\* Different from asthma,  $p < 0.01$ .

\*\*\*\* Different from asthma,  $p < 0.001$ .



**Fig 9** Sleep efficiency index in 20 stable asthmatics, 34 age-matched healthy subjects, 7 "pink puffers", and 13 "blue bloaters".



**Fig 10** Relationship between the overnight fall in forced expiratory volume in 1 second (FEV<sub>1</sub>) and total sleep time in 18 stable asthmatics. The overnight change in FEV<sub>1</sub> is expressed in litres in the upper figure and as a percentage of the pre-sleep FEV<sub>1</sub> in the lower figure. The regression (solid) line and 95% confidence limits for the measurements (dashed line) are indicated.

### 3(iii) Relation between overnight fall in FEV<sub>1</sub> and sleep in the

asthmatic patients: Although the asthmatic patients slept less well than their age-matched control subjects, there was no clear relationship between the overnight change in FEV<sub>1</sub> (expressed either in litres or as a percentage of the pre-sleep FEV<sub>1</sub>) and either the total sleep time (fig 10) or the sleep efficiency index.

## 4. Apnoea and hypopnoea during sleep

As in normal subjects (see Chapter 6), apnoea and hypopnoea occurred much more frequently in the asthmatics than did hyperpnoea. Although episodes of hyperpnoea followed by a respiratory pause (possibly representing sighs) were seen in three of the asthmatic patients during intervening periods of wakefulness, only two episodes of hyperpnoea, both in the same subject, were observed during actual sleep and they were not associated with any significant change in arterial oxygen saturation or in EEG sleep stage. Hyperpnoea is therefore not considered further.

The prevalence of apnoea and hypopnoea in the asthmatic patients showed the normal tendency to increase with age, 253 of the 329 episodes of apnoea and hypopnoea recorded in the 20 asthmatic patients occurring in the 8 subjects over the age of 40 yr ( $p < 0.001$ ). As in the normal subjects there was no sex difference in the prevalence of apnoea and/or hypopnoea during sleep.

**4(i) Asthmatics vs normal subjects:** During the time spent asleep, there was no significant difference between the asthmatics and the

normal subjects in either the number of apnoeas, the number of hypopnoeas, the total number of apnoeas plus hypopnoeas or the number of minutes of irregular breathing, either per night or per hour of sleep (table 5).

**4(ii) Asthmatic patients vs patients with chronic bronchitis and**

**emphysema:** Breathing patterns during sleep were similar in the asthmatic patients and bronchitic patients, with no significant difference in the prevalence of apnoea and/or hypopnoea, or the total duration of irregular breathing, either between the asthmatic patients and the "pink puffers" or between the asthmatic patients and the "blue bloaters" (table 5).

**5. Arterial oxygen saturation**

The prevalence of nocturnal hypoxaemia in the asthmatic patients showed the normal tendency to increase with age, 30 of the 45 hypoxaemic episodes (67%) in the asthmatic patients occurring in the 8 subjects over 40 years of age ( $p < 0.01$ ). As in normal subjects there was no sex difference in either the number of hypoxaemic episodes per night or the lowest arterial oxygen saturation during sleep.

**5(i) Asthmatics vs normal subjects:** The mean arterial oxygen saturation when awake averaged 95.4% (range 91 - 98%) in the asthmatics, but 97.0% (range 94 - 99%) in the age-matched healthy subjects ( $p < 0.001$ ; table 5). Hypoxaemia during sleep was both more common and more pronounced in the asthmatics. Hypoxaemic

episodes occurred 0 - 7 (mean 2.3) times per night in the asthmatics and 0 - 5 (mean 0.4;  $p < 0.001$ ) times per night in the normal subjects (table 5). The mean lowest  $\text{SaO}_2$  during sleep was 86.0% (range 77 - 94%) in the asthmatics, whereas this was 92.8% (range 72 - 96%;  $p < 0.001$ ) in the healthy controls (table 5; fig 11). The mean fall in  $\text{SaO}_2$  from the level awake to the lowest level during sleep was 9.4% (4 - 19%) in the asthmatics and 4.2 (2 - 24%;  $p < 0.001$ ) in the control subjects (table 5).

**5(ii) Asthmatic patients vs patients with chronic bronchitis and**

**emphysema:** The  $\text{SaO}_2$  awake, the maximal fall in  $\text{SaO}_2$  during sleep, the number of hypoxaemic episodes, and the lowest  $\text{SaO}_2$  recorded during sleep were each similar in the asthmatic patients and the "pink puffers" (table 5; fig 11). In contrast, the "blue bloaters", who had lower levels of arterial oxygen saturation when awake (mean 78.2%, range 60 - 89%) than the asthmatic patients (mean 95.4%, range 91 - 98%;  $p < 0.001$ ), had much greater falls in  $\text{SaO}_2$  during sleep (mean 25.9%, range 18 - 47%) than did the asthmatics (mean 9.4%, range 4 - 19%;  $p < 0.001$ ; table 5; fig 11). The lowest  $\text{SaO}_2$  during sleep in the "blue bloaters" averaged 52.4% (range 30 - 75%) compared to 86.0% (range 77 - 94%;  $p < 0.001$ ) in the asthmatic patients (table 5; fig 11).

These results suggested that the largest falls in arterial oxygen saturation during sleep tended to occur in the subjects who had the lowest levels of  $\text{SaO}_2$  when awake. The relationship between the level of oxygenation during wakefulness and the lowest level of

oxygenation during sleep was therefore explored further, using data from all 80 subjects studied in this way i.e. all 40 normal subjects described in Section II, together with the 20 asthmatic patients and the 20 bronchitic subjects.

#### 6. Relationship between the level of oxygenation when awake and the lowest level of oxygenation during sleep

When the data for the normal subjects, the asthmatics, the "pink puffers" and the "blue bloaters" were plotted together, there was a clear and curvilinear relationship between the arterial oxygen saturation during wakefulness and the lowest arterial oxygen saturation measured during sleep (fig 12a). When the calculated arterial oxygen tensions were plotted, there was a significant linear correlation ( $p < 0.001$ ; fig 12b) between the calculated  $\text{PaO}_2$  during wakefulness and the lowest calculated  $\text{PaO}_2$  during sleep, with the equation:

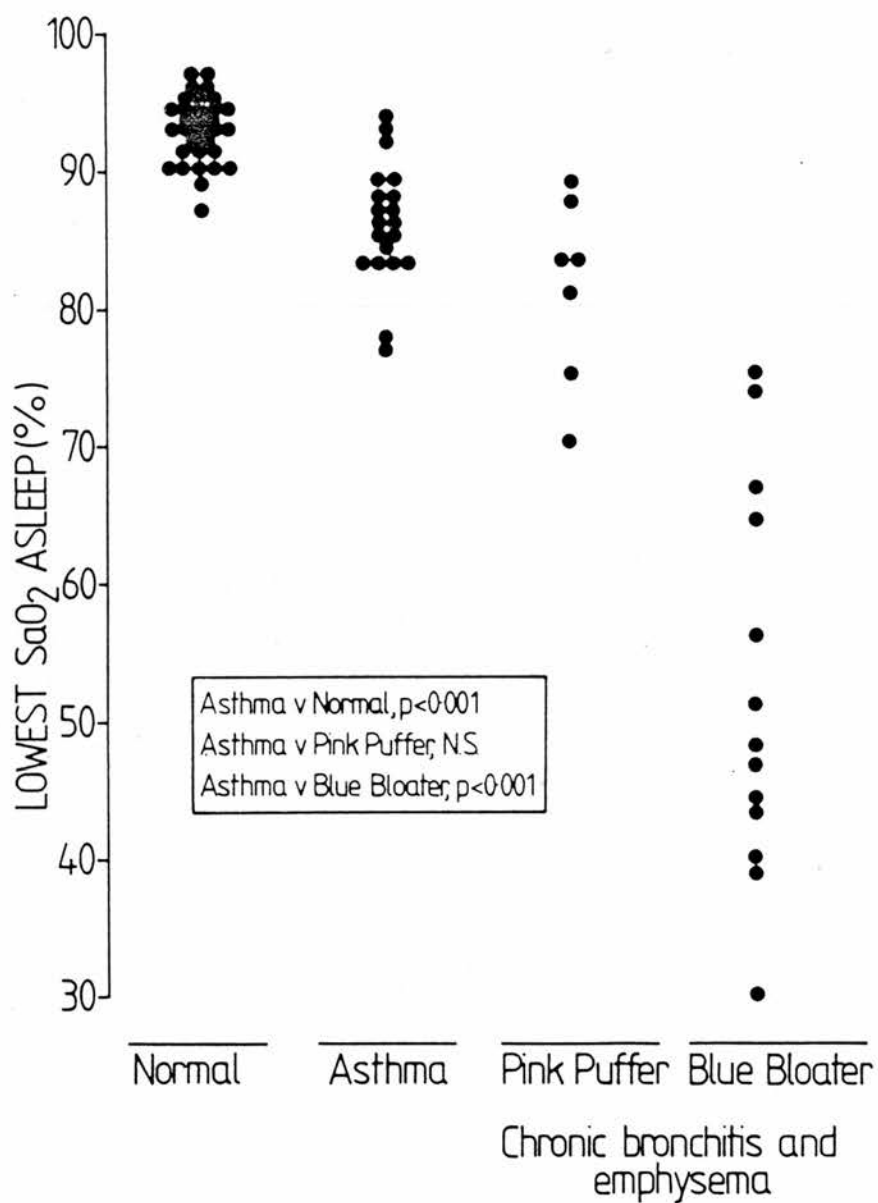
$$\text{PaO}_2 \text{ asleep (kPa)} = 0.58 \times \text{PaO}_2 \text{ awake (kPa)} + 1.06$$

$$n = 80; r = 0.83; p < 0.001$$

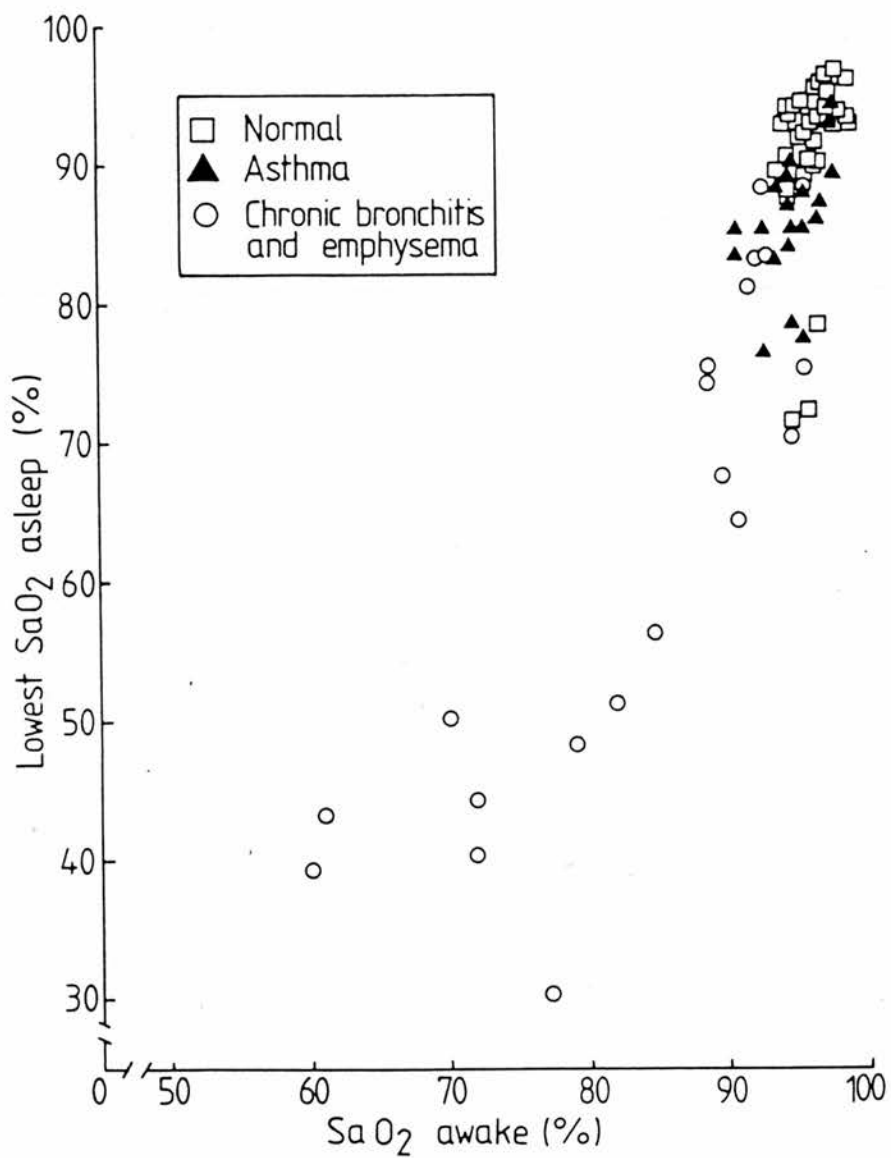
#### 7. Arterial oxygen tension

The calculated maximal fall in arterial oxygen tension during sleep in the asthmatic patients was  $3.6 \pm 0.3$  kPa. This was not significantly different from that of either the normal subjects, or the "pink puffers", and it was actually greater than the calculated  $\text{PaO}_2$  fall in the "blue bloaters" (table 5). When expressed as a proportion of the  $\text{PaO}_2$  when awake, however, the calculated fall in

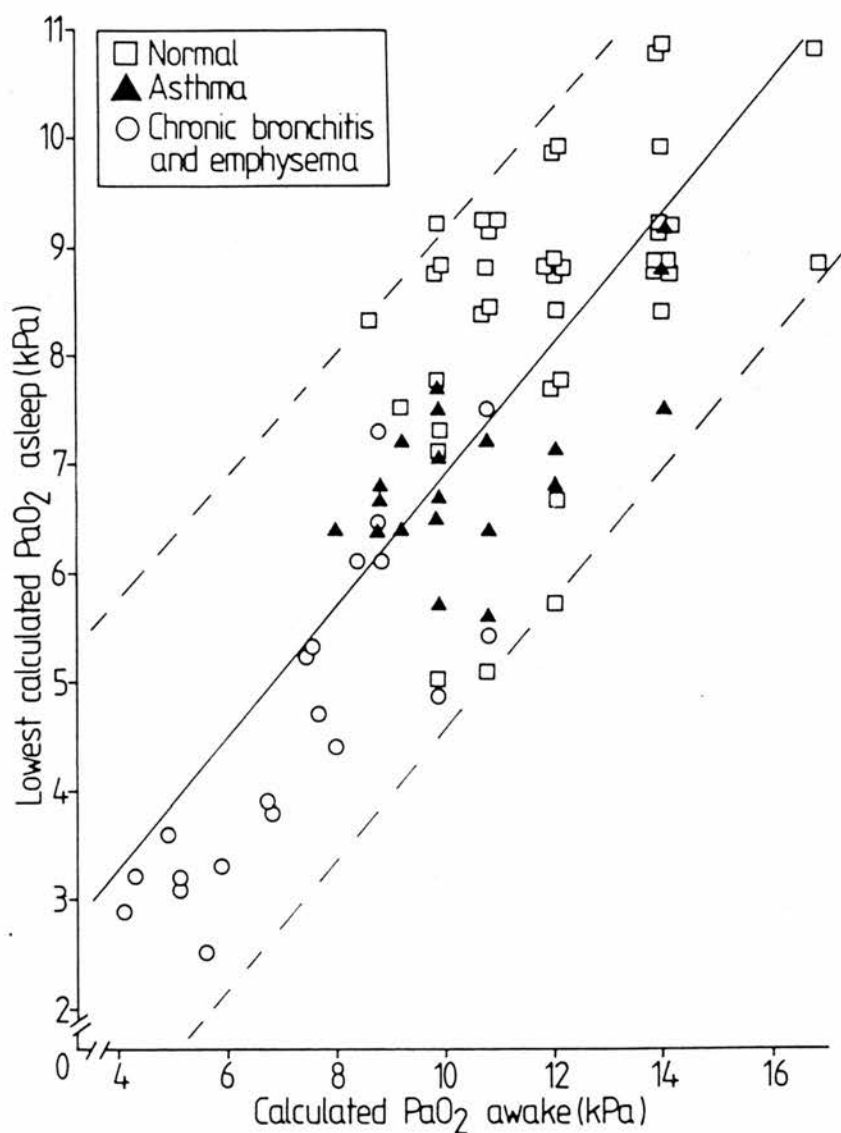




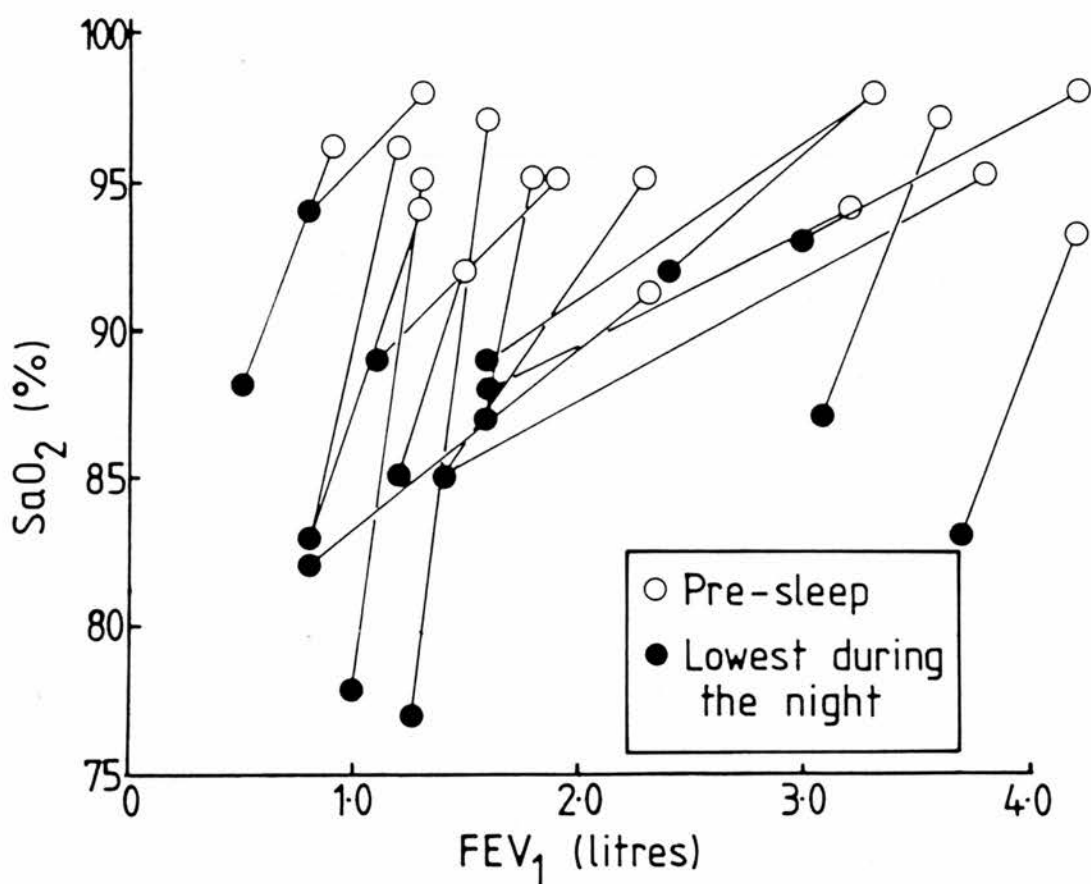
**Fig 11** Lowest arterial oxygen saturation during sleep (ear oximeter) in 20 stable asthmatics, 34 age-matched healthy subjects, 7 "pink puffers" and 13 "blue bloaters".



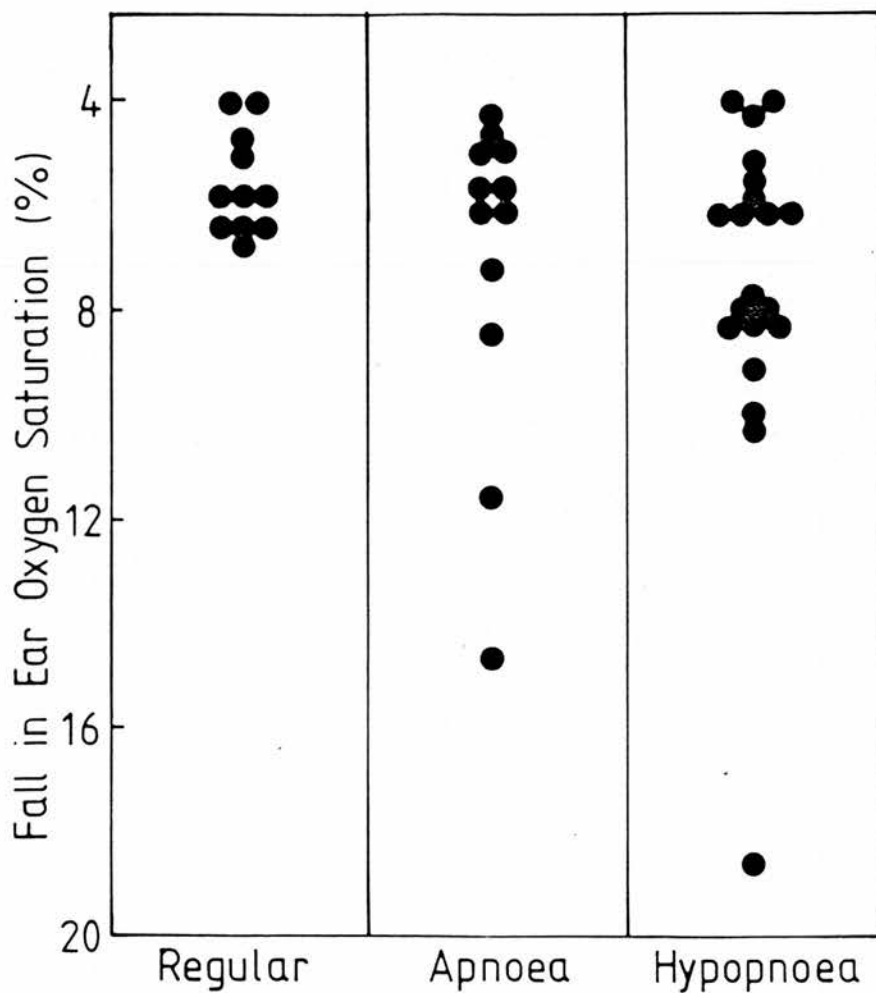
**Fig 12a** Relationship between the arterial oxygen saturation (SaO<sub>2</sub>) when awake and the lowest SaO<sub>2</sub> during sleep in 40 healthy subjects, 20 stable asthmatics and 20 patients with chronic bronchitis and emphysema.



**Fig 12b** Relationship between the calculated arterial oxygen tension ( $\text{PaO}_2$ ) when awake and the lowest calculated  $\text{PaO}_2$  during sleep in 40 healthy subjects, 20 stable asthmatics and 20 patients with chronic bronchitis and emphysema. The regression (solid) line and 95% confidence limits for the measurements (dashed line) are shown.



**Fig 13** Relationship between the overnight fall in FEV<sub>1</sub> (FEV<sub>1</sub> before sleep - FEV<sub>1</sub> after sleep) and the overnight fall in arterial oxygen saturation (ear oximeter) in 18 stable asthmatics.



**Fig 14** Relationship between breathing patterns and arterial oxygen desaturation (ear oximeter) in asthmatic patients. Each point represents a hypoxaemic episode. The fall in arterial oxygen saturation is from the stable level during sleep.

PaO<sub>2</sub> in the asthmatics was no different from that of any of the other three groups of subjects (table 5).

#### 8. Relationship between nocturnal hypoxaemia and overnight fall in FEV<sub>1</sub> in the asthmatic patients

There was no correlation between the maximal fall in arterial oxygen saturation during sleep and the overnight change in FEV<sub>1</sub> in the asthmatic patients (fig 13).

#### 9. Sleep stage during hypoxaemic episodes in the asthmatic patients

Most (30/45) of the hypoxaemic episodes (67%) occurred during REM sleep which occupied, on average, 15.8% of total sleep time. In only two patients was the rate of occurrence of hypoxaemic episodes in NREM sleep greater than in REM sleep ( $p < 0.001$ ). Thirteen of the remaining 15 hypoxaemic episodes occurred during stage 2 sleep and one during stage 1 sleep (appendix; table 19).

#### 10. Breathing pattern during hypoxaemic episodes in the asthmatic patients

Most (32/43) of the hypoxaemic episodes (74%), including those with the greatest falls in arterial oxygen saturation (fig 14), occurred during hypopnoea (20 episodes) or apnoea (12 episodes). In 6 of the remaining 11 episodes, the breathing pattern showed a cyclical pattern with recurrent falls in the amplitude of chest movement, but these reductions in chest movement were not sufficient to satisfy our strict criteria for hypopnoea. During two of the hypoxaemic episodes, the breathing pattern could not be determined because the

magnetometer trace was of poor quality.

## **11. Computer analysis of breathing pattern**

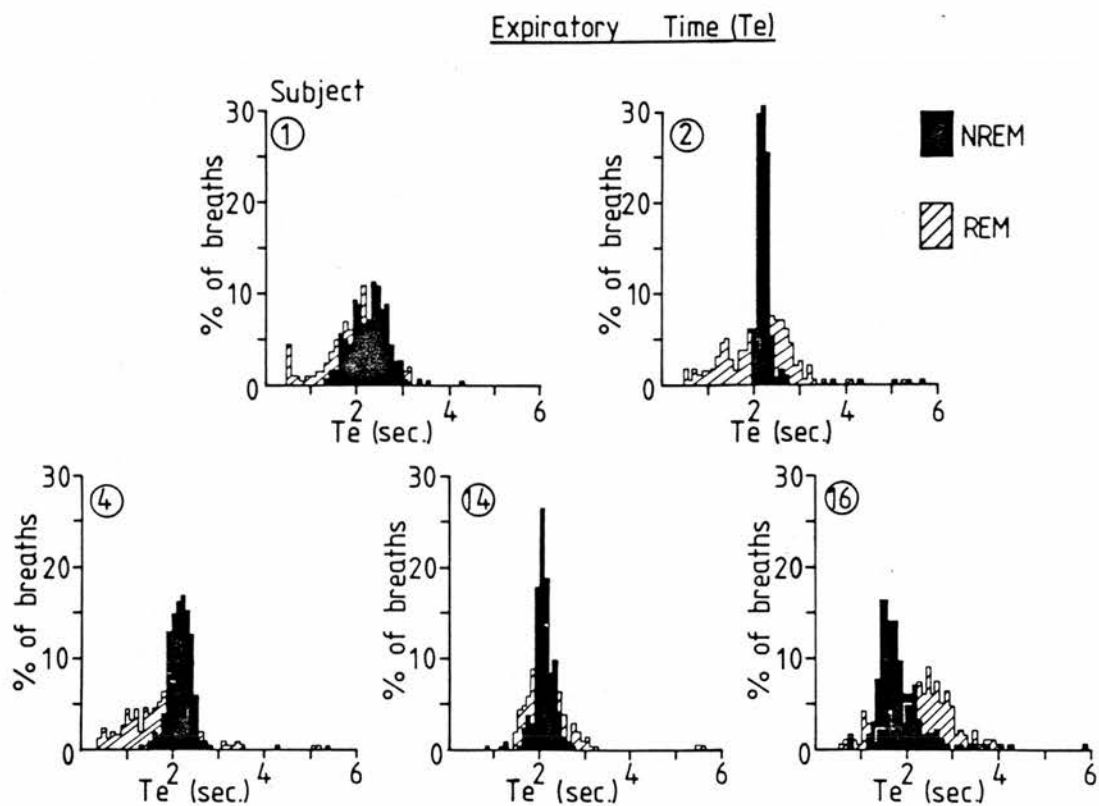
Examples of the frequency histograms obtained from the computer analysis of the breathing patterns are shown in fig 15. The results for all the patients studied in this way are summarised in figs 16 and 17.

**11(i) Changes between NREM sleep and REM sleep:** During REM sleep, there was a fall in the amplitude of chest movement ("Vt") compared with NREM sleep, but this change was similar in the asthmatics and the control subjects (fig 16a). There was no significant change in respiratory timing in either group (fig 16a).

In both groups the breathing pattern became more variable during REM sleep, as shown by an increase in the coefficient of variation (mean/standard deviation) of all the variables measured (fig 16b). This variability was similar in the asthmatics and the control subjects (fig 16b).

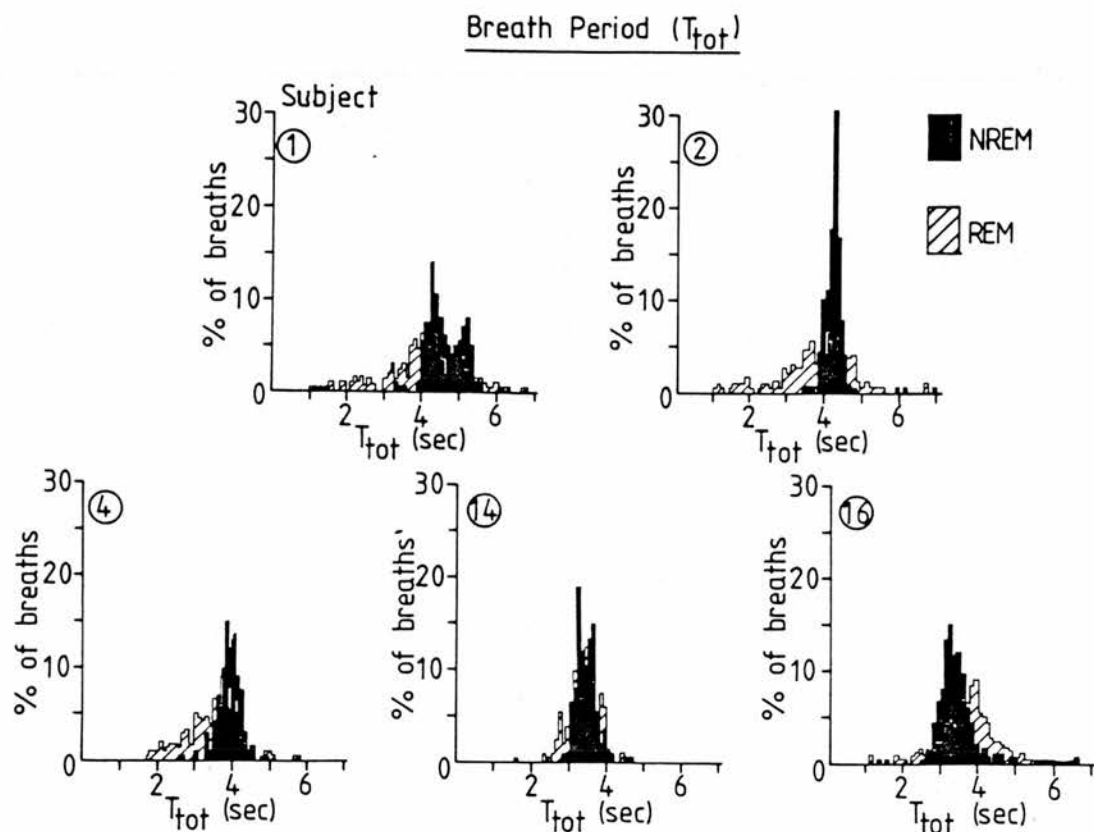
### **11(ii) Changes between NREM sleep at 1 am and NREM sleep at 4 am:**

There were no significant changes in any measure of respiratory timing between NREM sleep at 1 am and NREM sleep at 4 am, either in the asthmatic patients or in the control subjects (fig 17). Although the asthmatic patients had evidence of nocturnal bronchoconstriction (overnight fall in  $FEV_1$   $0.9 \pm 0.8$  l in these 6 patients), there was no significant increase in expiratory time ( $T_e$ )

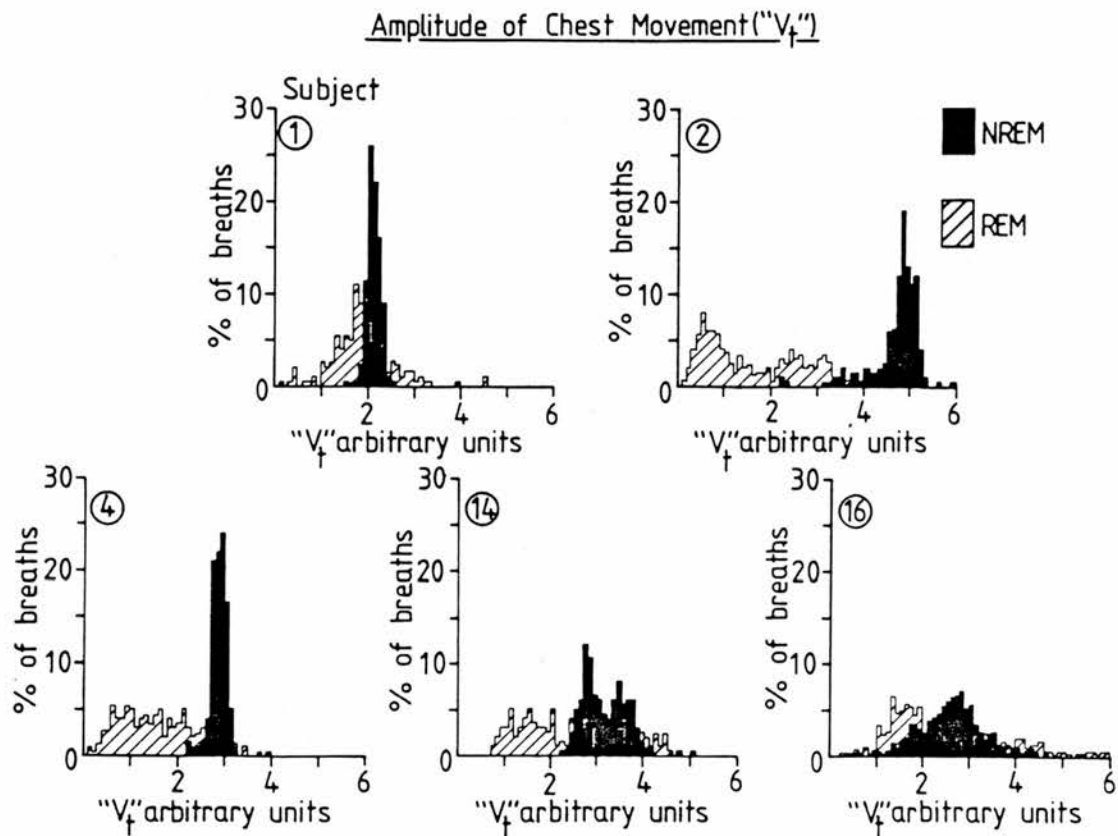


**Fig 15a** Frequency histograms of expiratory time for each breath during a 10-15 minute period of REM sleep and an adjacent 10-15 minute period of NREM sleep in 5 patients with asthma. See text for details.

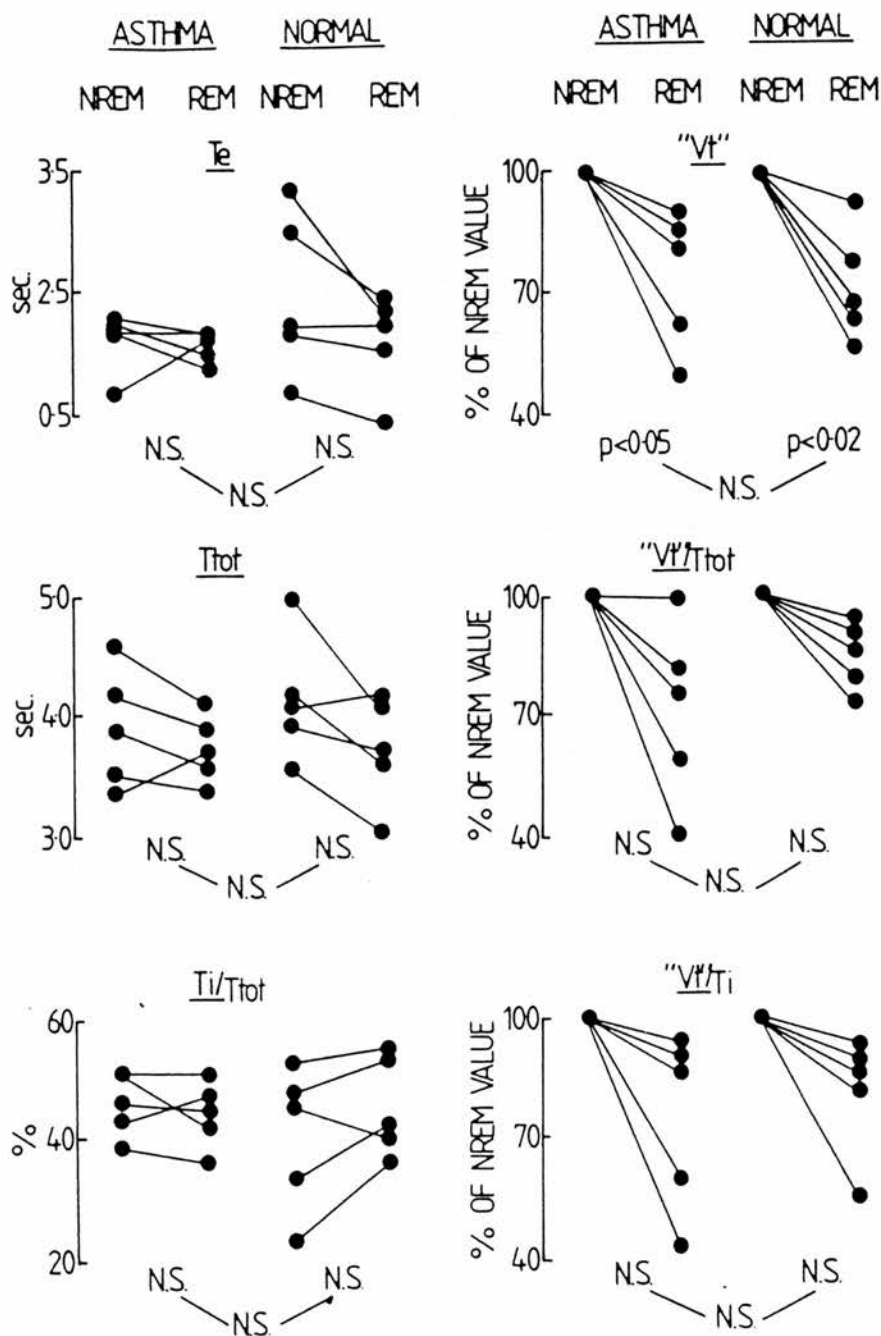




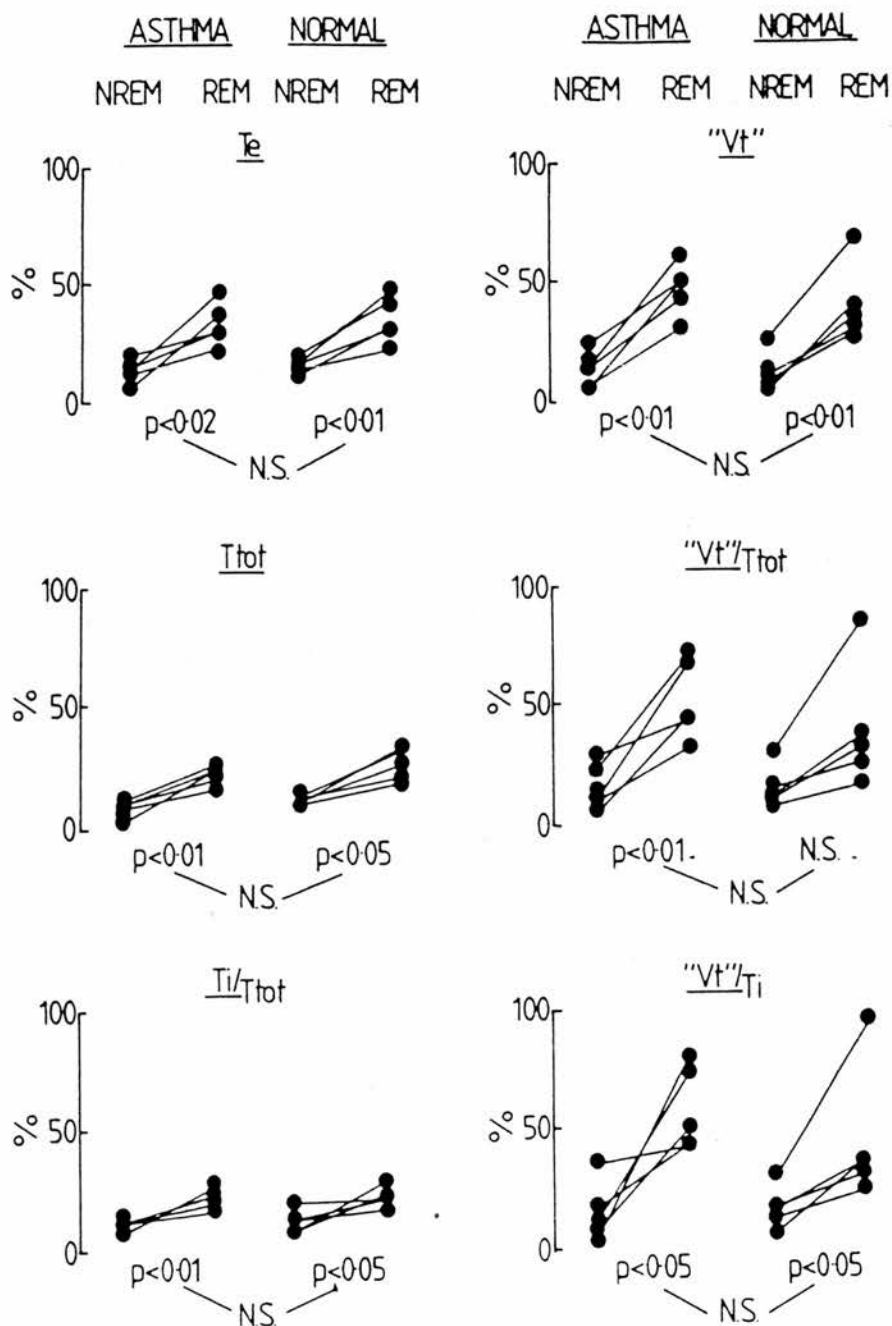
**Fig 15b** Frequency histograms of breath period for each breath during a 10-15 minute period of REM sleep and an adjacent 10-15 minute period of NREM sleep in 5 patients with asthma. See text for details.



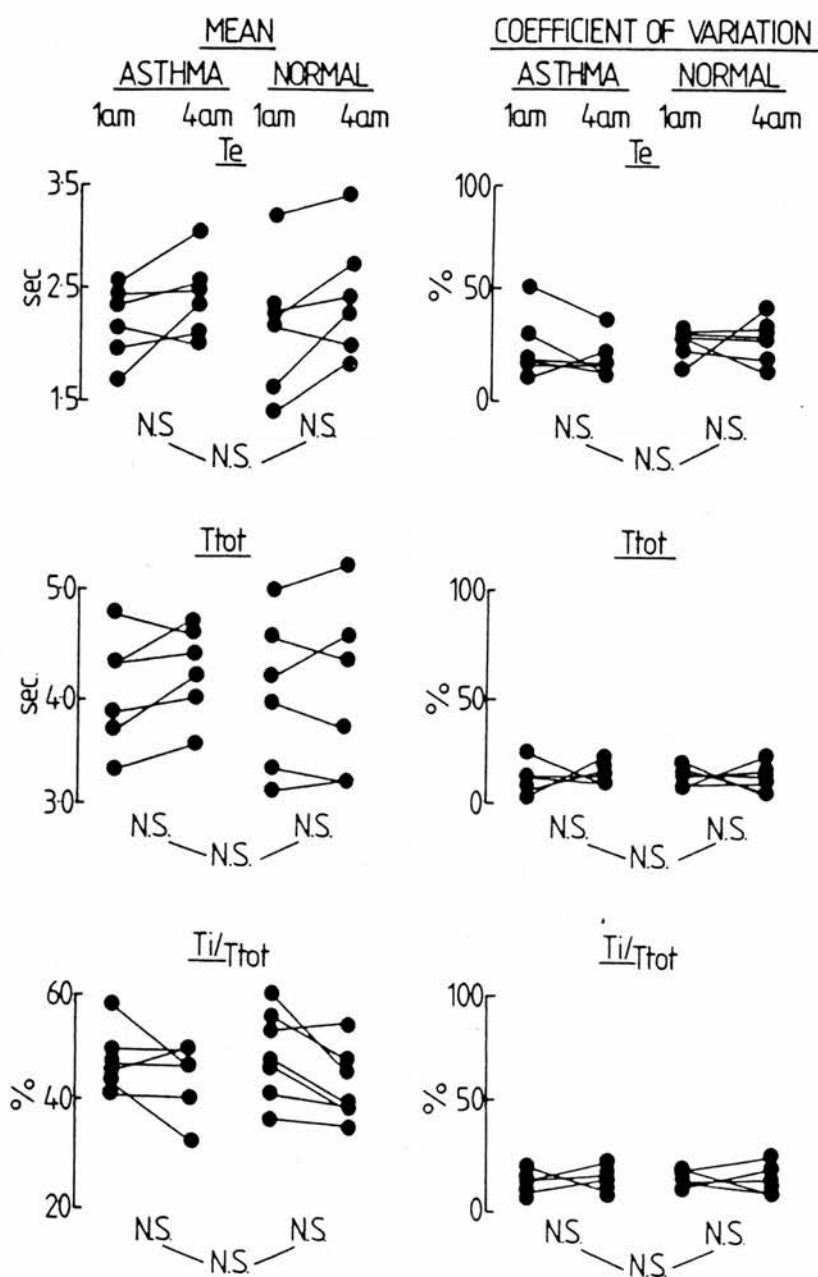
**Fig 15c** Frequency histograms of amplitude of chest movement for each breath during a 10-15 minute period of REM sleep and an adjacent 10-15 minute period of NREM sleep in 5 patients with asthma. The breaths analysed were the same as those in figs 15a and 15b.



**Fig 16a** Breathing patterns during REM and NREM sleep. The figures shown are the mean values of expiratory time ( $T_e$ ), breath period ( $T_{tot}$ ), respiratory duty cycle ( $T_i/T_{tot}$ ), amplitude of chest movements (" $V_t$ "), "ventilation" (" $V_t$ "/ $T_{tot}$ ) and "inspiratory flow rate" (" $V_t$ "/ $T_i$ ) during NREM sleep and an adjacent period of REM sleep in 5 asthmatics and 5 control subjects. The number of breaths analysed in the asthmatics was  $227 \pm 12$  in NREM sleep and  $246 \pm 12$  in REM sleep. The number of breaths analysed in the control subjects was  $208 \pm 8$  in NREM sleep and  $219 \pm 8$  in REM sleep.



**Fig 16b** Breathing patterns during REM and NREM sleep. The figures shown are the coefficients of variation (mean/standard deviation) of the variables shown. The breaths analysed were the same as those in fig 16a.



**Fig 17** Breathing patterns at 1 am and 4 am. The figures shown are the means and coefficients of variation (mean/standard deviation), of expiratory time ( $T_e$ ), breath period ( $T_{tot}$ ), and respiratory duty cycle ( $T_i/T_{tot}$ ) during NREM sleep at 1 am and NREM sleep at 4 am in 6 stable asthmatics and 6 control subjects. See text for details. The number of breaths analysed in the asthmatics was  $227 \pm 12$  at 1 am and  $190 \pm 8$  at 4 am. The number of breaths analysed in the control subjects was  $225 \pm 10$  at 1 am and  $214 \pm 12$  at 4 am.

during the night. Mean  $T_e/T_{tot}$  decreased by an average of 8% between 1 am and 4 am; this was not different from the 12% in the control group.

## DISCUSSION

The asthmatic patients in this study slept less well and became more hypoxaemic during sleep than did healthy subjects of the same age. However, their nocturnal breathing patterns were normal.

### Sleep

The pattern of sleep disruption in our asthmatic patients was similar to that reported in previous (Kales et al, 1968) and concurrent (Montplaisir et al, 1982) studies of stable adult asthmatics. The main abnormalities were an increase in the amount of time spent awake, a decrease in sleep efficiency and a decrease in total sleep time. There was also an increase in the percentage of total sleep time spent in stage 1 sleep at the expense of deeper stages of sleep, although the percentage of total sleep time spent separately in each of stages 2, 3, 4 and REM was not significantly different in the controls and asthmatics. As in other studies (Kales et al, 1968 and 1970; Montplaisir et al, 1982; Issa and Sullivan, 1985), there was no clear relationship between EEG sleep stage and the requests from patients to use their inhalers during the night. All of our patients were in a relatively stable condition at the time of the study. Formal EEG recordings of sleep have not been made during acute attacks of asthma, but patients' own reports and clinical

observation suggest that they sleep even less well when they are acutely ill.

The consequences of sleep disruption in patients with asthma have not been studied. Studies in normal subjects indicate that sleep deprivation causes impaired daytime vigilance (reviewed in Parkes, 1985), and this could be a potential problem in asthmatics, especially asthmatic children who are still at school. Sleep disruption for 24 hours can also reduce ventilatory drive (Cooper and Phillips, 1982; White et al, 1983; Schiffman et al, 1983). During acute attacks of asthma, when patients often have several worsening nights with little or no sleep, such a blunting of drive could be a factor, along with fatigue and continuing bronchospasm, in the subsequent development of hypoxaemia and hypercapnia in some of these patients (Tai and Read, 1966; McFadden and Lyons, 1968).

The modest nocturnal hypoxaemia in our patients was unlikely to be the cause of their sleep disruption, for the arousals did not occur during episodes of hypoxaemia. There is debate whether severe hypoxaemia can disrupt sleep (Brezinova et al, 1982; Calverley et al, 1982; Fleetham et al, 1982), but studies in normal human subjects (Berthon-Jones and Sullivan, 1982; Douglas et al, 1982b; Gothe et al, 1982) and in animals (Phillipson et al, 1978; Bowes et al, 1980; Nebauer et al, 1981), indicate that modest hypoxaemia very rarely causes arousal. It is more likely that sleep disruption in the asthmatic patients was a direct consequence of their bronchospasm since Montplaisir and colleagues (1982) found that asthmatics slept

better when their overnight bronchoconstriction was relieved. Not all bronchodilators improve sleep, however. Theophyllines can actually disrupt sleep in patients with airflow limitation (Fleetham et al, 1983; Rhind et al, 1985). The effects of bronchodilator drugs on sleep, breathing and oxygenation at night in patients with asthma are discussed in chapter 9.

### **Breathing patterns**

The asthmatic patients had no more apnoea and hyponoea during sleep than their age-matched healthy control subjects, an observation which has also been made in concurrent studies in other laboratories (Montplaisir et al, 1982; Neagley et al, 1986). As in normal subjects, the prevalence of apnoea and hypopnoea increased with age and was the same in both sexes.

One of the clinical signs of an acute attack of asthma is relative prolongation of expiration (Batten, 1978; Fraser and Parre, 1979), and lengthening of expiratory time has also been described, using respiratory inductive plethysmography, during bronchoconstriction induced by histamine (Stewart et al, 1984a). I postulated, therefore, that it might be possible to detect bronchoconstriction during sleep without waking asthmatic patients, by studying their spontaneous breathing patterns. However, there were no significant changes in expiratory time, inspiratory time or breath period between 1 am and 4 am in the asthmatics, despite overnight bronchoconstriction. These results do not totally exclude changes in spontaneous breathing pattern during sleep resulting from



nocturnal bronchoconstriction, however, since we did not actually measure bronchoconstriction while the patients were asleep. Furthermore, our patients had only moderate overnight changes in FEV<sub>1</sub>, and we measured only chest movement. Issa and Sullivan (1985), using a respiratory inductive plethysmograph to measure both thoracic and adominal movement, recently demonstrated phase changes between the chest and abdomen during acute attacks of asthma in four sleeping subjects. Morgan and colleagues (1986), in a similar study of nine asthmatic patients, found no phase changes during sleep but their patients apparently had less severe nocturnal asthma than those of Issa and Sullivan for none woke with acute attacks of asthma during the study, although they did show an overnight fall in FEV<sub>1</sub> from a mean of 2.6 litres to a mean of 1.9 litres. Spontaneous breathing patterns, therefore, seem unlikely to be useful for assessing mild or moderate bronchoconstriction during sleep. It is possible that studies of thoraco-abdominal movement may be useful in detecting the onset of severe nocturnal asthma, but further studies will be needed to confirm this.

The reduction in chest movement, and corresponding falls in "inspiratory flow rate" and "minute ventilation", which occurred during REM sleep were also unlikely to be due to REM-related bronchoconstriction in the asthmatic patients (see chapter 11), since similar changes in breathing pattern were seen in the normal subjects during REM sleep. Paradoxical indrawing of the rib cage has been described during REM sleep in adolescent asthmatics, aged 12-15 years (Tabachnik et al, 1981), but this has not been confirmed in

adult stable asthmatics (Morgan et al, 1986). This question of paradox could not be addressed in the present study, since only chest movement was measured, at the level of the third intercostal space anteriorly.

For the same reason, tidal volume and ventilation could not be assessed accurately in this study (see Chapter 2). Nevertheless, the results of both hand analysis and computer analysis of the magnetometer signal clearly suggested that there was hypoventilation during REM sleep, without alteration in respiratory rate, both in the asthmatics and the normal subjects. This finding is in agreement with concurrent studies of ventilation during sleep in asthmatics, (Tabachnik et al, 1981; Morgan et al, 1986) and normal subjects (Douglas et al, 1982, Krieger et al, 1983b; Stradling et al, 1985). In contrast, Hudgel and colleagues (1984), in a study of six normal adults, found no changes in ventilation, tidal volume or breath frequency between NREM and REM sleep, and Tabachnik and co-workers (1981a), in nine normal adolescent subjects, found that tidal volume and ventilation tended to increase from NREM to REM. Both these studies involved respiratory inductive plethysmography but the results were based on analysis of epochs of only 20 breaths (Hudgel et al, 1984) or one minute (Tabachnik et al, 1981a). Analysis based on such short epochs could lead to errors in the estimation of ventilation during REM sleep, for, in our experience the periodicity of the typical breathing pattern in REM sleep (waxing and waning of chest movement), is often greater than one minute.

## Oxygenation

The observation that stable asthmatics have modest, but nevertheless abnormal, arterial oxygen saturation during sleep is in agreement with the results of concurrent studies in both asthmatic children (Smith and Hudgel, 1980) and asthmatic adults (Montplaisir et al, 1982). In the present study, the falls in arterial oxygen saturation during sleep in the asthmatic patients were greater than those of normal subjects, similar to those of "pink puffers", and less than those of "blue bloaters". However, the calculated changes in arterial oxygen tension were similar in all four groups. In each group, most of the hypoxaemic episodes were associated with hypopnoea during REM sleep. In asthma, therefore, as in chronic bronchitis and emphysema (Catterall et al, 1985), nocturnal hypoxaemia in REM sleep is probably due mainly to hypoventilation, although the present study does not exclude co-existent changes in ventilation/perfusion balance (Fletcher et al, 1983). Such hypoventilation is normal in REM sleep (Douglas et al, 1982; Stradling et al, 1985), and patients with asthma and chronic bronchitis and emphysema have greater falls in arterial oxygen saturation than normal subjects mainly because they start the night at a lower point on the oxyhaemoglobin dissociation curve. Although asthmatic patients bronchoconstrict overnight, with possible worsening of the bronchoconstriction during REM sleep (see Chapter 11), this did not appear to cause significant additional hypoxaemia in our relatively stable asthmatics, at least as assessed by the maximal overnight fall in arterial oxygen tension. There was no clear relationship between the overnight fall in  $FEV_1$  and the maximal fall in arterial oxygen saturation in the asthmatic

patients.

The observation that there is a linear relationship between the lowest oxygen tension during sleep and the oxygen tension during wakefulness has a number of implications.

First, these results mean that it is probably unnecessary to perform sleep studies on patients with asthma or chronic bronchitis and emphysema to see how much they desaturate - within moderately wide limits (fig 12) that can be predicted from their arterial oxygen tension when awake. There may be exceptions to this, however, since the sleep apnoea syndrome can occasionally coexist with obstructive pulmonary disease (Guilleminault et al, 1980; Goldstein et al, 1984; Flenley, 1985). Patients suspected of having both these conditions - because of daytime hypersomnolence (Guilleminault et al, 1980) or because of morning headaches after receiving nocturnal oxygen (Goldstein et al, 1984) - should have studies of breathing and oxygenation during sleep because they may benefit from relief of their sleep apnoea, e.g. by continuous nasal positive airways pressure (Sullivan et al, 1981). The sleep apnoea syndrome has not yet been described in a patient with asthma, but there appears to be no reason why the two conditions could not coexist.

Second, it confirms that sleep hypoxaemia is a continuum from health to disease. During acute attacks of asthma, therefore, when patients often have daytime hypoxaemia (Tai and Read, 1966; McFadden and Lyons, 1968; Rees et al, 1968), patients would be expected to

have greater falls in arterial oxygen saturation during sleep than were recorded in this study, and such hypoxaemia could contribute to the rare but tragic nocturnal deaths from acute asthma. However, there have been no actual measurements of oxygenation during sleep in patients who are hypoxaemic due to acute asthma. Ideally, such studies would involve patients who were breathing air without supplemental oxygen, and this would be difficult to justify ethically during acute attacks of asthma. Furthermore, sleep studies are complex, with numerous pieces of equipment, and they would pose many practical problems in asthmatic patients who are acutely ill. Studies of a patient with chronic daytime hypoxaemia due to asthma are described in chapter 7.

Third, these results suggest that any treatment which improves daytime oxygenation would be expected to reduce nocturnal hypoxaemia. Thus, they emphasise the importance of regular daytime treatment in asthma, a principle which also applies to the prevention of overnight bronchoconstriction (Horn et al, 1985, see Chapter 13). Bronchodilators given only at night have not been shown to improve oxygenation during sleep in asthma (Catterall et al, 1983; Stewart et al, 1984; Rhind et al, 1985; Neagley et al, 1986). From figure 12, it would also be predicted that oxygen could be used to reduce nocturnal hypoxaemia in asthma, as it is known to do in hypoxic chronic bronchitis and emphysema (Douglas et al, 1979a). This point is also addressed in chapter 7.

## Chapter 7

### **BREATHING AND OXYGENATION DURING SLEEP IN AN ASTHMATIC PATIENT WITH PERSISTENT DAYTIME HYPOXAEMIA**

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The stable asthmatics studied in chapter 6 had relatively normal levels of oxygenation during wakefulness, with modest falls in arterial oxygen saturation during sleep. It was postulated that asthmatics who were more hypoxaemic when awake would have greater falls in arterial oxygen saturation during sleep. However, this hypothesis was based largely on observations in patients with hypoxic chronic bronchitis and emphysema. This chapter contains studies of a patient with chronic daytime hypoxaemia due to asthma. The results show that this patient had severe nocturnal hypoxaemia, which occurred during periods of hypoventilation in REM sleep. Because of the unusual severity of this patient's hypoxaemia together with carbon dioxide retention and cor pulmonale, we also studied his ventilatory responses to oxygen and carbon dioxide when awake.

#### Patient

A 20 year old man was referred so that his suitability for domiciliary oxygen therapy could be assessed. In early childhood he

had developed intermittent wheeze and nocturnal cough, with severe flexural eczema. Despite treatment with sodium cromoglycate, and later with inhaled salbutamol and inhaled beclomethasone, he had rarely been free of symptoms. He had lost time from school each year because of asthma, and his best FEV<sub>1</sub> recorded up to the age of 19 had been 1.0 litre.

Six months prior to referral, at the age of 19, he had been admitted to hospital with an exacerbation of asthma, associated with hypoxaemia, hypercapnia, and clinical evidence of right ventricular failure. Although the FEV<sub>1</sub> had risen to 1.9 litres with nebulised bronchodilators and oral prednisolone, it had subsequently fallen again after discharge and he had remained hypoxaemic with carbon dioxide retention.

At the time of referral his symptoms were relatively stable. He gave no family history of respiratory illness and he denied ever having smoked. He did not have regular sputum production and there was no history of previous pneumonia, whooping cough, haemoptysis or calf pain. His regular medication consisted of inhaled beclomethasone, inhaled salbutamol, frusemide with supplemental potassium, and digoxin.

On examination he was plethoric but had no signs of cardiac failure. The chest was hyperinflated and there were a few scattered high pitched rhonchi.

The chest radiograph showed enlargement of the pulmonary conus but no cardiomegaly and no pruning of peripheral blood vessels. The electrocardiogram showed incomplete right bundle branch block. While breathing air, the arterial oxygen tension was 7.3 kPa with an arterial carbon dioxide tension of 7.0 kPa and a hydrogen ion concentration of 44 nmol/l. While breathing 30% oxygen, the arterial oxygen tension rose to 9.4 kPa, with an arterial carbon dioxide tension of 7.4 kPa. Haemoglobin concentration in the peripheral blood was 19.3 g/dl, the white cell count was  $8.7 \times 10^9/l$  of which 11% were eosinophils, and the red cell mass was 34.6 ml/kg (normal 22-28 ml/kg). Pulmonary arterial pressure (PAP) was 40/15 mmHg, mean 22 mmHg (normal mean 12-18 mmHg). The FEV<sub>1</sub> was 1.3 litres (predicted 4.1, SD 0.5 litres) and the FVC 1.6 litres (predicted 4.8, SD 0.6 litres). Total lung capacity measured by helium dilution was normal but the residual volume and the residual volume/total lung capacity ratio (RV/TLC) were each approximately twice normal. The transfer factor for carbon monoxide was low normal at 8.4 mmol/min/kPa (predicted 11.3, SD 1.7). Skin prick tests to six allergens including Dermatophagoides pteronyssinus, Aspergillus fumigatus, and cat fur were strongly positive. Tests for Aspergillus precipitins were negative. The sweat test for cystic fibrosis was normal (sodium 26.9 mmol/l, potassium 10.8 mmol/l) and the serum level of alpha-1 antitrypsin was normal at 3.0 g/l (reference range 1.8-4.0 g/l).

#### Studies of breathing and oxygenation during sleep

Electroencephalographic sleep stage, chest movement, oronasal



airflow, and ear oxygen saturation were monitored non-invasively as described in Section II, on three consecutive nights. The first night was for acclimatisation only. On the second night, the patient breathed air at 2 l/min by nasal prongs and on the third night oxygen at the same flow rate, in a single blind protocol.

#### Studies of ventilatory control when awake

These studies were performed by Dr P Calverley, with my assistance. On the morning before the first night's sleep study the ventilatory response to progressive isocapnic hypoxia was measured in duplicate at the patient's resting end-tidal carbon dioxide tension, using the method of Weil and colleagues (1970) as modified by Calverley and co-workers (1983). The ventilatory response to hypercapnia was measured during steady state conditions in a background of hyperoxia (end-tidal oxygen tension > 25 kPa) with an inspired carbon dioxide concentration of 2% and subsequently 5% (Lloyd et al, 1958). The results are expressed as instantaneous minute ventilation ( $\dot{V}_t \times f = \dot{V}_e \text{ inst}$ ) per percentage fall in ear oxygen saturation ( $\dot{V}_e/\text{SaO}_2$ ) or per kilopascal rise in end-tidal carbon dioxide tension ( $\dot{V}_e/\text{PETCO}_2$ ).

#### Studies with medroxyprogesterone acetate

Both the sleep studies and the studies of ventilatory control were repeated after four weeks of treatment with the ventilatory stimulant medroxyprogesterone acetate (MPA) 20 mg eight-hourly. The sleep studies were repeated once more after a total of eight months' treatment with MPA.

## RESULTS

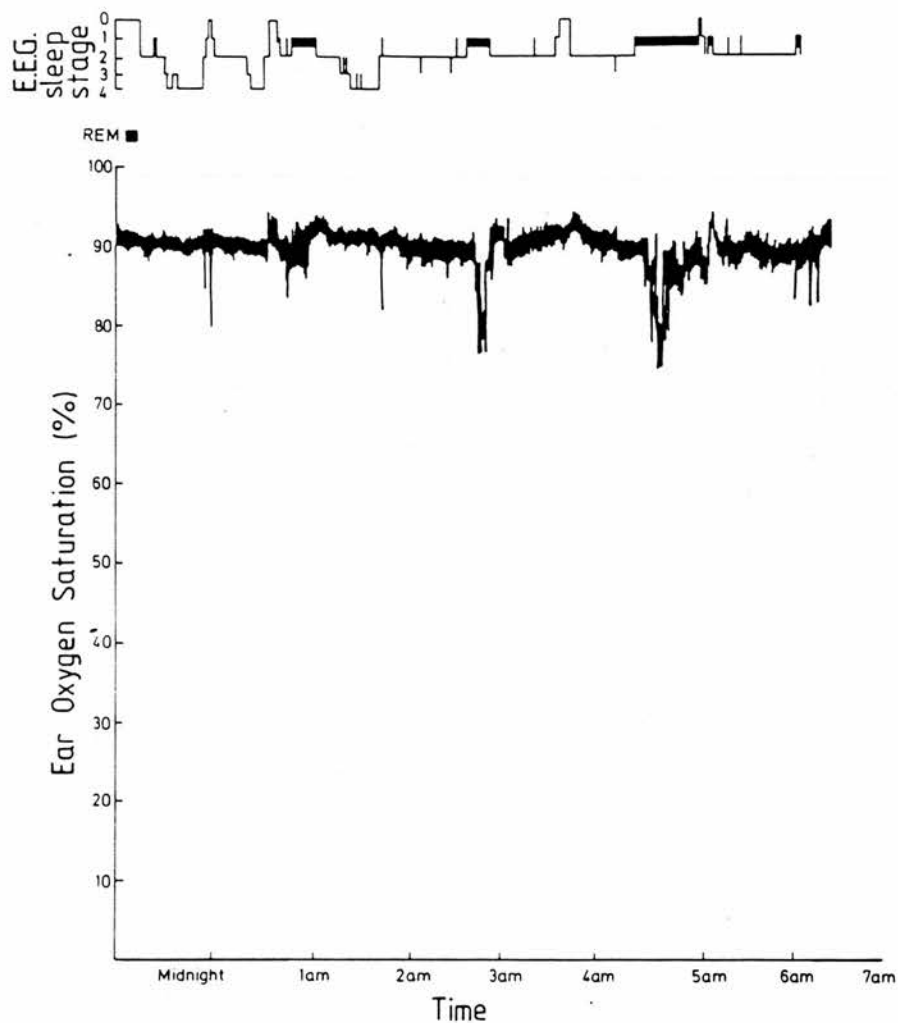
### Sleep studies

In all the studies the patient's total sleep time, and the percentage of REM sleep were similar to those of other asthmatic patients (Chapter 6; table 6).

When breathing air,  $\text{SaO}_2$  fell from 92% during wakefulness to 76% at the lowest level during sleep. There were numerous 4% falls in  $\text{SaO}_2$  (see chapter 5), and on three occasions during the night (two of them in REM sleep)  $\text{SaO}_2$  fell transiently by 10% or more (fig 18; table 6). Treatment with medroxyprogesterone acetate had no significant effect on nocturnal oxygenation (table 6). When breathing oxygen, however, the arterial oxygen saturation remained above 91% throughout the night. There were no episodes of sleep apnoea either before or after therapy, and all the hypoxaemic episodes occurred during periods of recurrent hypopnoea as defined in Section II. Hypopnoea was as frequent during the oxygen treatment nights as during the air studies.

### Ventilatory control studies

The ventilatory response to hypoxia, both before and after treatment with medroxyprogesterone acetate, was well below the average for normal subjects (Douglas et al, 1982b; Calverley et al, 1983). The ventilatory response to carbon dioxide doubled after treatment with MPA for four weeks, but even at this level, it was at the lower limit of the normal range (Hirshmann et al, 1975).



**Fig 18** Arterial oxygen saturation (ear oximeter) and EEG sleep stage throughout the night in a 20 year old asthmatic patient who was hypoxic when awake.

TABLE 6

**OXYGENATION, NOCTURNAL SLEEP, AND VENTILATORY CONTROL  
MEASUREMENTS BEFORE AND AFTER MEDROXYPROGESTERONE ACETATE  
IN AN ASTHMATIC PATIENT WITH PERSISTENT DAYTIME HYPOXAEMIA**

	Stable SaO <sub>2</sub> awake	Lowest SaO <sub>2</sub> asleep	10% falls in SaO <sub>2</sub>	TST (min)	REM (% of TST)	$\dot{V}_e$ / SaO <sub>2</sub> (l/min)	$\dot{V}_e$ / PETCO <sub>2</sub> (l/min)
Pre-progesterone (air night)	92.0	76.0	3	410	20.1	0.07	3.67
Pre-progesterone (O <sub>2</sub> night)	97.0	91.5	0	423	17.6	-	-
After 4 weeks progesterone (air night)	91.0	77.0	1	375	20.2	-0.10	7.62
After 8 months progesterone	90.0	75.2	4	343	21.2	-	-

SaO<sub>2</sub>, ear oxygen saturation (%); TST, total sleep time; REM, rapid eye movement sleep,  $\dot{V}_e$ /SaO<sub>2</sub>, change in ventilation per unit % fall in SaO<sub>2</sub>;  $\dot{V}_e$ /PETCO<sub>2</sub>, change in ventilation per kPa rise in end-tidal CO<sub>2</sub>.

### Follow-up

Because of the response to oxygen treatment, the patient was given domiciliary oxygen, to take for 15 hours daily, including the sleeping hours (Medical Research Council Working Party, 1981). He felt less tired with this treatment but his condition continued to deteriorate slowly and he died, out of hospital, 28 months after starting oxygen treatment. Permission for autopsy was declined.

### DISCUSSION

Despite the youth of this patient, and despite the fact that he was in a stable condition, he had more severe nocturnal hypoxaemia than any of the asthmatic patients described in Chapter 6. Apart from the night that he received oxygen, the patient showed a relatively constant pattern of nocturnal hypoxaemia, with arterial oxygen saturation falling to an average lowest value of 76%, corresponding to an arterial oxygen tension of 5.5 kPa (assuming normal body temperature and pH, see Chapter 6). These values are more commonly seen in patients with hypoxic chronic bronchitis and emphysema or patients with recurrent sleep apnoea.

In Chapter 6, I postulated that nocturnal falls in arterial oxygen saturation could be much more marked during acute attacks of asthma - when patients are hypoxaemic by day - than during relatively stable periods. I also postulated that oxygen would be effective in relieving such nocturnal hypoxaemia. A study to confirm these

postulates would be difficult to justify on ethical grounds, however, since it would involve denying oxygen to patients at night during acute attacks of asthma. The patient described above had asthma, with no evidence of other respiratory disease, and he also was hypoxaemic by day. Although the daytime hypoxaemia of this patient was due to chronic disease rather than an acute attack of asthma, his large nocturnal falls in  $\text{SaO}_2$  and their correction by oxygen lend support to the above postulates.

As in other subjects (Chapter 4, 6), the nocturnal hypoxaemic episodes in this patient were associated with reduced chest movement. The fact that he continued to hypoventilate despite marked nocturnal hypoxaemia suggests that his ventilatory response to hypoxia was reduced during REM sleep. There have been no measurements of ventilatory drive during sleep in asthmatic patients, but studies in normal subjects indicate that the ventilatory responses to both hypoxia (Berthon-Jones and Sullivan, 1982; Douglas et al, 1982b; Hedemark and Kronenberg, 1982) and hypercapnia (Birchfield et al, 1959; Bulow, 1963; Gothe et al, 1981; Douglas et al, 1982c) are reduced during sleep, with the most marked decreases occurring in REM sleep. This patient had blunted ventilatory responses to hypoxia and hypercapnia when awake, and these blunted responses presumably played a permissive role in the pathogenesis of his marked nocturnal hypoxaemia. Patients with hypoxic chronic bronchitis and emphysema, who also have large falls in arterial oxygen saturation during sleep, also tend to have low ventilatory responses to hypoxia (Flenley et al, 1970; Kepron and Cherniack, 1973) and hypercapnia (Kepron and

Cherniack, 1973; Matthews, 1977; Bradley et al, 1979) when measured during wakefulness.

Hudgel and Weil (1974) also reported a teenage asthmatic boy with a low hypoxic ventilatory drive, and their patient also had persistent hypoxaemia with carbon dioxide retention and cor pulmonale. In their patient, there was evidence for a hereditary deficiency in ventilatory drive and the authors suggested that this may have predated the onset of severe airways obstruction. There is also evidence from other studies that the ventilatory responses to hypoxia (Collins et al, 1978) and hypercapnia (Mountain et al, 1978) may be strongly influenced by genetic factors. We attempted to pursue this possibility in our patient, by approaching members of his immediate family for study of their ventilatory drives. However, they did not wish to undertake such studies. We cannot say, therefore, whether the low ventilatory responses to hypoxia and hypercapnia in our patient were due to hereditary factors or whether they were a consequence of prolonged hypoxia, as described in patients living at altitude (Severinghaus et al, 1966; Milledge and Lahiri, 1967) and in patients with cyanotic congenital heart disease (Sorensen and Severinghaus, 1968; Edelman et al, 1970).

Cor pulmonale is rare in asthma. In chronic bronchitis and emphysema, there is evidence that nocturnal hypoxaemia may contribute to the pathogenesis of cor pulmonale (see Chapter 5). We did not measure pulmonary arterial pressure during the night in this patient, but it seems likely that the recurrent nocturnal hypoxaemic episodes

in this patient contributed to the development of pulmonary hypertension and subsequent right ventricular failure.

Medroxyprogesterone acetate stimulates ventilation during wakefulness in normal subjects (Skatrud et al, 1978; Zwillich et al, 1978) and in patients with chronic obstructive pulmonary disease (Skatrud et al, 1980; Dolly and Block, 1983). It has also been shown to improve oxygenation during sleep in patients with chronic mountain sickness (Kryger et al, 1978) and to raise the arterial carbon dioxide tension during NREM sleep in patients with chronic obstructive pulmonary disease (Skatrud et al, 1981). I was therefore interested to know whether medroxyprogesterone acetate would improve nocturnal oxygenation in this patient. Treatment with medroxyprogesterone acetate for four weeks, at a dose which has been shown to stimulate ventilation during wakefulness and NREM sleep in chronic obstructive pulmonary disease (Skatrud et al, 1981), was associated with a doubling of his ventilatory response to hypercapnia during wakefulness, but it had no effect on either the hypoxic ventilatory drive when awake, or on the severity of nocturnal hypoxaemia. Even after four further weeks of treatment, the nocturnal hypoxaemia was unchanged. Medroxyprogesterone acetate has also proved to be disappointing in the treatment of nocturnal hypoxaemia in patients with chronic bronchitis and emphysema. In a recent double-blind controlled trial of the drug in 19 patients with chronic obstructive pulmonary disease (Dolly and Block, 1980), there was no significant difference in either the number of episodes of desaturation or the lowest arterial oxygen saturation during sleep between the active



drug and placebo.

On the other hand, nocturnal oxygen was effective in reducing nocturnal hypoxaemia in this patient, and he was therefore given domiciliary oxygen. He died 28 months after starting this treatment. In the recent UK Medical Research Council trial of domiciliary oxygen in hypoxic chronic bronchitis and emphysema (Medical Research Council Working Party, 1981), approximately 60% of male patients receiving oxygen 15 hours daily survived longer than this, and in the American trial of home oxygen therapy (Nocturnal Oxygen Therapy Trial Group, 1980), 50% of bronchitic patients receiving nocturnal oxygen, and 75% receiving continuous oxygen, survived longer than 28 months. Thus, our patient's survival time, following commencement of domiciliary oxygen, was similar to that of many patients with severe chronic bronchitis and emphysema after starting this treatment.

It must be stressed that although this patient had asthma, with evidence of no other respiratory disease, the course of his illness was atypical. Nevertheless, the studies described above illustrate that severe nocturnal hypoxaemia can occur in asthma, in association with daytime hypoxaemia, and that this nocturnal hypoxaemia may be of grave significance.

## Chapter 8

### THE EFFECTS OF KETOTIFEN IN NOCTURNAL ASTHMA

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Assessment of the efficacy of drugs in nocturnal asthma has largely been restricted to measurements of airway calibre (Soutar et al, 1975; Milledge and Morris, 1979; Reinhardt et al, 1980; Fairfax et al, 1980; Connolly, 1981; Barnes et al, 1982; Carpentiere et al, 1983; Horn et al, 1984), with the recent exception of a study by Davies and colleagues (1984) who used a subjective scoring system to assess sleep quality in patients receiving theophyllines. It would clearly be of interest also to know the effects of such drugs on EEG sleep patterns and sleep related hypoxaemia in asthmatic patients, particularly as some bronchodilators can have direct effects on the central nervous system. Beta agonists and theophyllines, for example, are central nervous system stimulants and could therefore disrupt sleep directly, whilst ketotifen, a relatively new drug which has been advocated for the treatment of asthma, often causes drowsiness and potentially, therefore, could aggravate hypoxaemia. These drugs have recently been studied in our laboratory to determine their effects on sleep, breathing patterns and oxygenation at night in patients with asthma. The studies with ketotifen are described

in this chapter. The other studies - with choline theophyllinate (Rhind et al, 1985), terbutaline (Stewart et al, 1984) and disodium cromoglycate (Morgan et al, 1985) - will not be described in detail in this thesis as they were performed mainly by other workers.

## **METHODS**

Non-invasive measurements of EEG sleep stage, breathing patterns, arterial oxygen saturation ( $\text{SaO}_2$ ), and overnight change in  $\text{FEV}_1$  were made during nocturnal sleep in 10 adult patients with stable asthma, in a double-blind crossover trial of ketotifen.

### **Patients**

The patients (9 men and 1 woman), aged 18 - 55 years all had airways obstruction that was reversible and varied spontaneously. During the two years before the study the lowest  $\text{FEV}_1$  recorded in these subjects at the out-patient clinic ranged from 0.5 to 1.9 l and the highest spontaneous  $\text{FEV}_1$  from 1.7 to 4.2 l. Eight of the patients had positive skin prick test responses to at least two common allergens, and six had a family history of atopy. All the patients used a  $\beta_2$  agonist inhaler, six took beclomethasone dipropionate by inhalation and three took regular oral prednisolone in a dose of 5 mg daily. None of the patients was receiving sodium cromoglycate, antihistamines, theophyllines, hypnotics, or sedatives. Most (7) of the patients had never been studied in the sleep laboratory before, but three had taken part in the study described in chapter 6 at least one year earlier, and of these 3, 2 received ketotifen first and 1

received placebo first.

### Protocol

The trial was designed so that half the patients received placebo before ketotifen and half received ketotifen first. The patients slept in a quiet darkened room on two pairs of two consecutive nights (the first night in each pair serving as an acclimatisation night) separated by two to four weeks.

On the night of the study  $\beta_2$  agonists were withheld from 5 pm. The patients arrived in the laboratory at 9.30 pm and, after the apparatus had been set up and the  $FEV_1$  measured, they were given one tablet of either placebo or ketotifen ten minutes before the lights were switched off. During the night EEG sleep stage, chest movement, oronasal airflow and arterial oxygen saturation were measured as described previously (Section II). In the morning the  $FEV_1$  was measured when the patient woke up.

Differences between placebo and ketotifen nights were analysed by the paired Student's "t" test. Values are given as mean  $\pm$  standard errors of the mean.

## RESULTS

### Arterial oxygen saturation

$SaO_2$  during sleep was unaltered by ketotifen. The change in  $SaO_2$

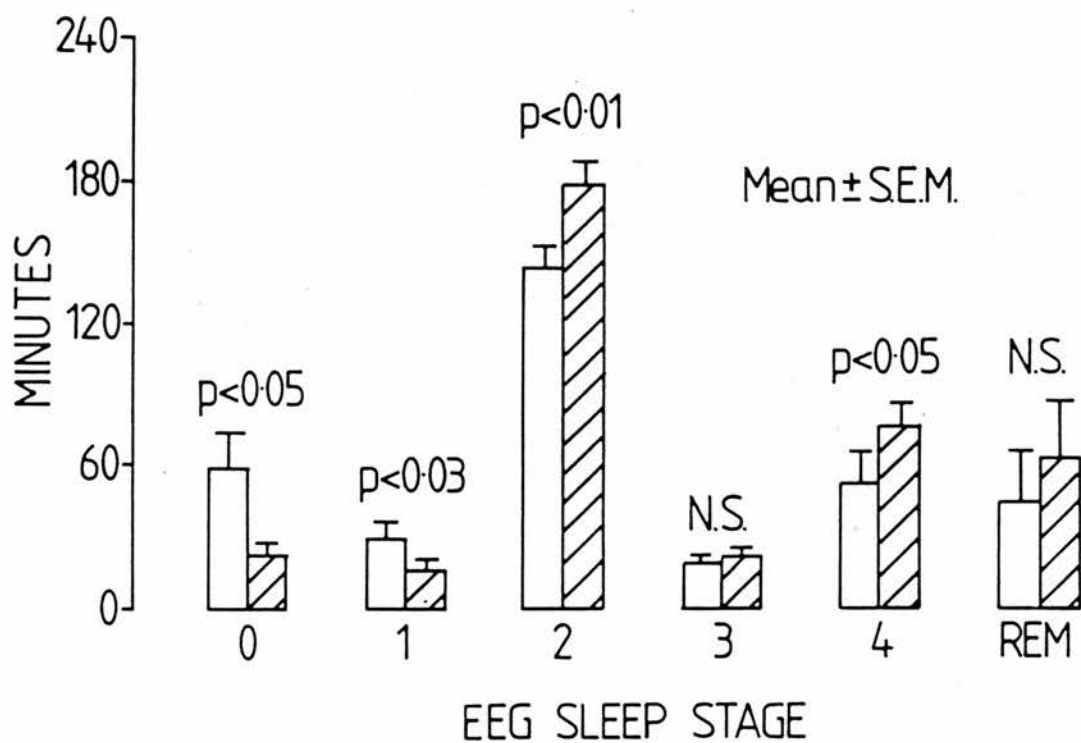
from the level before sleep (ketotifen nights  $96.4 \pm 0.7\%$ ; placebo nights  $95.6 \pm 0.9\%$ ) to the lowest level during sleep (ketotifen  $88.4 \pm 1.2\%$ ; placebo  $88.1 \pm 1.6\%$ ) was the same after the drug ( $8.0 \pm 1.1\%$ ) and after placebo ( $7.8 \pm 1.2\%$ ). Significant episodes of hypoxaemia ( $\text{SaO}_2$  falls of at least 4% from the immediately preceding stable  $\text{Sao}_2$ ) occurred in six patients from 1 to 9 times (mean 2.4 times) per night on placebo. The number of episodes was not significantly different on ketotifen nights, when 6 patients had from 1-12 (mean 2.6) hypoxaemic episodes per night.

### Irregular breathing

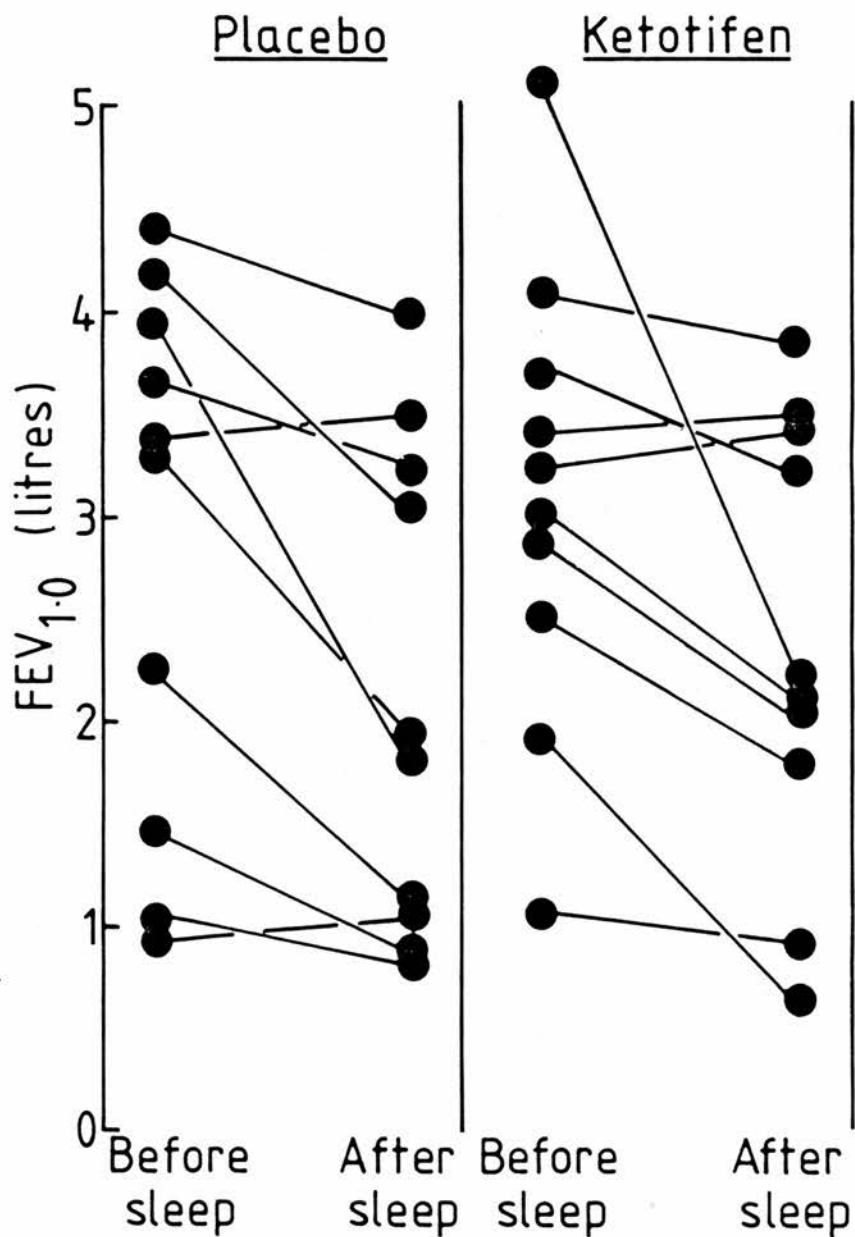
The cumulative duration of irregular breathing during sleep (apnoeas and hypopnoeas; chapter 5) was the same on ketotifen and placebo nights averaging  $42 \pm 12$  min after the active drug and  $37 \pm 7$  min after placebo. Most (99%) of this irregular breathing was hypopnoea. In all ten subjects only 9 episodes of apnoea occurred after placebo and 11 after ketotifen.

### EEG sleep stages

Total sleep time occupied  $387 \pm 8$  min on ketotifen nights but only  $336 \pm 19$  min on placebo nights ( $p < 0.02$ ). When expressed as a percentage of time in bed (sleep efficiency index), this true sleep occupied  $95 \pm 1.1\%$  of time in bed on the ketotifen nights but only  $85 \pm 3.8\%$  of time in bed on the placebo nights ( $p < 0.04$ ). On ketotifen nights, less time was spent in EEG sleep stages 0 ( $p < 0.05$ ) and 1 ( $p < 0.03$ ), and more time in EEG sleep stages 2 ( $p < 0.01$ ) and 4 ( $p < 0.01$ ) than on placebo nights (fig 19). The time



**Fig 19** Duration of different EEG sleep stages in 10 stable asthmatics studied during sleep after taking placebo (open bars) or 1 mg ketotifen (standard bars).



**Fig 20** Forced expiratory volume in 1 second (FEV<sub>1</sub>) measured before sleep and after sleep on placebo nights (left) and when the patients had taken 1 mg ketotifen (right). On the ketotifen nights, all the FEV<sub>1</sub> measurements after sleep were those made at the time of final awakening. On the placebo nights, 6 of the "after sleep" FEV<sub>1</sub> measurements were made at the time of final awakening and 4 were made when the patients woke during the night.

taken to fall asleep averaged 28 min on placebo nights compared to 12 min on ketotifen nights, but this was not a significant difference. The duration of stage 3 sleep (mean 21 min) and the duration of REM sleep (mean 55 min) were similar after drug and placebo (fig 19).

### Overnight change in FEV<sub>1</sub>

The FEV<sub>1</sub> before sleep averaged  $2.9 \pm 0.4$  l on ketotifen nights and  $2.9 \pm 0.4$  l on placebo nights. In all patients the lower of these values was within 30% of the higher. After taking ketotifen none of the patients asked to use an inhaler during the night. After taking placebo, however, 4 of the 10 patients asked to use their beta<sub>2</sub> agonist inhalers ( $p < 0.1$ , Chi<sup>2</sup> test for small numbers; Swinscow, 1976). After using their inhalers they went back to sleep. Three of these awakenings occurred between 3 and 3.30 am and the other at 5.35 am. The FEV<sub>1</sub> recorded at these times was on average 1.0 l (range 0.3 - 1.7 l) lower than the FEV<sub>1</sub> before sleep. In the other six patients the FEV<sub>1</sub> was on average 0.6 l lower after sleep than before sleep when they had taken placebo, compared with a fall of 0.9 l with ketotifen. This difference (fig 20) was not significant.

### DISCUSSION

The main purpose of this study was to determine whether ketotifen has adverse effects on breathing patterns and oxygenation during sleep in patients with asthma. The results show that ketotifen does not affect nocturnal breathing patterns and oxygenation, at least in stable asthmatics, when given as a single 1 mg dose.



However, ketotifen also had no significant effect on the overnight change in  $FEV_1$  in this study. Ketotifen has been described as protecting against acute antigen challenge (Pauwells et al, 1978; Wuethrich et al, 1978; Wells et al, 1979; Craps, 1981) and histamine challenge (Craps et al, 1978; Mattson et al, 1979; Beumer et al, 1979; Lisboa et al, 1985; Craps, 1981) in asthmatic patients but there is debate whether it provides effective prophylaxis against asthmatic attacks in clinical practice (Gobel, 1978; Lane, 1980; Dyson and Mackay, 1980; Petheram et al, 1981; Monie et al, 1982; Tinkelman et al, 1985). The observations of this study extend those of Dyson and Mackay who found that ketotifen in a daily dose of 2 mg for four weeks had no effect on patient's nocturnal dyspnoea, as assessed by diary cards.

Although ketotifen had no effect on oxygenation, breathing patterns or overnight change in  $FEV_1$ , it did help the patients to sleep. The patients slept longer and spent more time in the deeper stages of sleep after taking ketotifen than after taking placebo. It seems most likely that this is a direct effect on the central nervous system, for ketotifen has antihistaminic properties (Martin and Romer, 1978). Antihistamines in therapeutic dosage often cause somnolence (Harvey, 1975) but their effect on EEG sleep stages is poorly documented. Diphenhydramine, in contrast to ketotifen in this study, suppresses REM sleep (Rawl, 1980) but it is not known whether other antihistamines do the same.

Beta<sub>2</sub> agonists were withheld on the nights of the study, to separate the effects of ketotifen from those of sympathomimetic drugs. Whether ketotifen would have the same effects on EEG sleep stage when given in combination with beta agonists is not known. It is also not known whether the hypnotic effect of ketotifen persists in patients taking the drug for prolonged periods. It is probable that it does not, for daytime drowsiness in association with ketotifen usually resolves after two to three months' treatment (Craps, 1981; Tinkelman et al, 1985). In any event this hypnotic effect is unlikely to have a therapeutic application. Most if not all (Clark et al, 1971; Gaddie et al, 1972; Editorial, 1972) sedative drugs can depress respiration and although this would not be important in most stable asthmatics, it could aggravate respiratory failure during acute attacks of asthma. Although it is desirable to relieve the disturbed sleep of asthmatic patients (Chapter 6), I believe that, if possible, this should be achieved by agents which also relieve bronchoconstriction.

The oral drugs most frequently used to control the symptoms of nocturnal asthma are theophyllines and oral beta agonists. Although these agents reduce the overnight change in FEV<sub>1</sub> in asthmatic patients (Milledge and Morris, 1979; Fairfax et al, 1980; Barnes et al, 1982), they do not improve sleep (Fleetham et al, 1980; Stewart et al, 1984; Rhind et al, 1985), probably because of a direct stimulant effect. Indeed, recent studies in this laboratory (Rhind et al, 1985) indicate that theophyllines cause even more disruption of sleep than usual (see Chapter 6) in asthmatic patients. There

is a need for a bronchodilator which will remain effective throughout the night, and which will also relieve the disturbed sleep of asthmatic patients. This problem is discussed further in chapters 12 and 13.

### SUMMARY - PART III

The main aims of this part of the thesis were (i) to determine whether asthmatic patients become hypoxaemic at night and whether they have abnormal breathing patterns during sleep, (ii) to study the effects of asthma on sleep.

Three studies were performed:

1. Ear oxygen saturation ( $\text{SaO}_2$ ), oronasal airflow, chest movement and electroencephalographic sleep stage were monitored throughout an undisturbed night's sleep in 20 stable asthmatic patients and the results compared with those of similar studies in 34 age-matched healthy subjects. Since the asthmatic patients were more hypoxaemic than the normal subjects when awake, their nocturnal  $\text{SaO}_2$  falls were also compared to those of 20 patients with chronic bronchitis and emphysema.
2. In order to explore further the relationship between daytime oxygenation and oxygenation during sleep in asthma, studies were also performed in an asthmatic patient who was persistently hypoxaemic when awake.
3. In the third study, involving 10 patients, the effects of ketotifen on nocturnal oxygenation and breathing patterns in asthma were investigated.

The following results were obtained:

1. The patients with asthma became more hypoxaemic during sleep, with greater falls in  $\text{SaO}_2$ , than normal subjects of the same age.
2. The nocturnal  $\text{SaO}_2$  falls in the asthmatic patients were similar to those recorded in the "pink puffers" with chronic bronchitis and emphysema but much smaller than those recorded in "blue bloaters".
3. When expressed in terms of oxygen tension, the asthmatics, the normal subjects, the "pink puffers" and the "blue bloaters" all had similar changes in arterial oxygenation at night.
4. When the data for the normal subjects, the asthmatics, the "pink puffers" and the "blue bloaters" were plotted together, there was a linear relationship between the arterial oxygen tension when awake and the lowest arterial oxygen tension during sleep.
5. The asthmatic patient with persistent daytime hypoxaemia had much greater falls in  $\text{SaO}_2$  during sleep than other stable asthmatics of his age. This nocturnal hypoxaemia was corrected by oxygen but not by medroxyprogesterone acetate.
6. There was no clear relationship between the nocturnal fall in  $\text{SaO}_2$  and the overnight change in PEFV in the asthmatic patients.

7. Despite nocturnal bronchoconstriction, the asthmatic patients had normal breathing patterns during sleep, both in terms of the number of apnoeas and hypopnoeas per night and the duration of inspiration and expiration for each breath.
8. The patients with asthma slept less well than healthy subjects of the same age. They spent less of the night asleep, and the proportion of total sleep time spent in drowsiness (EEG sleep stage 1) was increased at the expense of the deeper stages of sleep.
9. Ketotifen, given in a single 1 mg dose at night, increased the duration and depth of sleep in asthmatic patients without affecting oxygenation or breathing patterns. However, it did not alter bronchoconstriction.

The implications of these results are as follows:

1. Patients with asthma become more hypoxaemic during sleep than healthy subjects of the same age because they start the night on a steeper part of the oxyhaemoglobin dissociation curve than normal.
2. Most stable asthmatic patients have relatively small nocturnal falls in  $\text{SaO}_2$  but patients with asthma who are hypoxaemic when awake may become markedly hypoxaemic during sleep. Nocturnal hypoxaemia in asthma can be corrected by oxygen.

3. Expensive studies of breathing and oxygenation during sleep do not appear to be indicated in the assessment of patients with asthma or chronic bronchitis and emphysema unless there is a coexistent sleep apnoea syndrome, since these patients have normal breathing patterns during sleep and the degree of nocturnal hypoxaemia can be predicted from the oxygen tension when awake.
4. There is a need for a bronchodilator which will act throughout the night without disrupting sleep.

**Part IV**

**THE RELATIONSHIP BETWEEN SLEEP AND NOCTURNAL  
BRONCHOCONSTRICTION**

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## Chapter 9

### REVIEW OF THE LITERATURE

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The idea that sleep may adversely affect asthma was stated clearly by Maimonides, in the twelfth century. In his treatise on asthma, Maimonides wrote:

"Sleep in this disease is rather harmful...Those afflicted should therefore sleep as little as possible."

However, Maimonides did not distinguish the effects of sleep itself from those of other circadian changes, nor could he attempt to distinguish an effect of sleep on bronchoconstriction itself from, say, sleep-related hypoventilation which also occurs in asthmatics (see chapter 6) or sleep-related hypoxaemia (chapter 6), since the concept of bronchoconstriction in asthma was not introduced until five centuries later (Willis, 1679).

In this chapter I shall review previous studies which have attempted to determine the relationship between sleep itself and actual airway narrowing.

## 1. General considerations

There is now considerable evidence that nocturnal bronchoconstriction in asthmatic patients represents an exaggeration of the normal circadian variation in airway calibre (see Chapter 1). Amplification of the normal rhythm is related to hyperreactivity of the airways, and there is a close relationship between the amplitude of "morning dipping" and bronchial reactivity to inhaled histamine (Ryan et al, 1982). This implies that the marked circadian change in bronchomotor motor tone in asthmatic patients is the result of their bronchial hyperreactivity, and that the underlying mechanism of nocturnal bronchoconstriction in asthma is likely to be the same as that which determines the overnight change in airway calibre of normal individuals.

Bronchial reactivity itself shows a circadian variation. Bronchoconstrictor responses to histamine (De Vries et al, 1962), to acetyl choline (Reinberg and Gervais, 1972) and to inhaled allergens (Gervais et al, 1977) are all lowest in the afternoon and greatest in the early morning or late at night. However, this circadian rhythm is unlikely to be the sole cause of nocturnal asthma since the circadian change in bronchial reactivity is no greater in asthmatics than in normal subjects (Reinberg and Gervais, 1972).

Many possible explanations for nocturnal asthma have been considered and it now seems likely that the pathogenesis of nocturnal bronchoconstriction is multifactorial (Barnes, 1984; Douglas 1985). This review will be confined to the relationship between nocturnal

bronchoconstriction and sleep. A more detailed review of nocturnal asthma (Douglas, 1985) and a recent symposium on this subject (Royal Society of Medicine, 1984), have been published elsewhere.

## 2. Does sleep cause bronchoconstriction?

Salter (1859) believed that sleep caused both an increase in reflex bronchoconstriction and a decrease in awareness of airflow limitation, and he attributed the efficacy of strong coffee in asthma to its stimulant effects. Writing on the "treatment of asthma by stimulants" he made the following observations (Salter, 1859):

"One of the commonest and best-reputed remedies of asthma is strong coffee.

....About the modus operandi of this remedy I was long puzzled; I could not make it out; and it is only lately that I have stumbled upon it.

....This fact is, that sleep favours asthma - that spasm of the bronchial tubes is more prone to occur during the insensibility and lethargy of sleep than during the waking hours, when the senses and will are active.

....Anything that rouses the asthmatic to a state of wakefulness will put a stop to asthma".

It was more than a century before Salter's hypothesis (that sleep disruption will improve nocturnal bronchoconstriction) was tested. Clark and Hetzel (1977) studied five asthmatic shift workers and found that the change from day shift to night shift was rapidly accompanied by inversion of the circadian rhythms in peak flow and that this "was complete by the time the first natural sleep had taken

place as each shift started". The inversion of the bronchoconstricting rhythm was felt to be more rapid than that reported for "basic" circadian rhythms such as body temperature or hormone levels (Perkoff et al, 1959), and the authors concluded that nocturnal bronchoconstriction is intimately related to sleep. However, the authors did not actually measure circulating hormone levels in relation to bronchoconstriction in these shift workers. Connolly (1981) reported similar findings.

Two years later, Hetzel and Clark (1979) reported another study in which they attempted to determine whether sleep causes bronchoconstriction. They studied patients in hospital who were recovering from an acute attack of asthma. The investigation contained three separate protocols, each involving sleep disruption.

In the first part of the study, five patients were woken for 15 minutes at 2 am and then allowed to go back to sleep. This did not affect the overnight fall in peak expiratory flow rate. However, this result does not exclude an effect of sleep on airway calibre, since the protocol involved only a very short period of sleep disruption.

In the second part of the study, five patients were woken at 2-hourly intervals to estimate the time of onset of the nocturnal fall in PEF. On a subsequent night they were woken 1 hour before that time, exercised for 15 minutes, and then allowed to go back to sleep. This procedure also failed to prevent a fall in PEF by 6 am, but

again the study only involved partial disruption of sleep.

In the third part of the study by Hetzel and Clark, eleven asthmatic patients were kept awake until 3, 4, or 5 am and then were allowed to sleep until 6 am. In six patients the "morning dip" in peak flow occurred prior to sleep, but in the other five most of the decrease in flow rate occurred during the 1 to 3 hours when sleep was allowed. Interpretation of this study is complicated by the fact that during the "awake" period the subjects "went to bed at 22.00 h and adopted the sleeping posture .... reading or listening to the radio". Most people would find it difficult to avoid snoozing when left like this until 5 am and it is not clear how scrupulously the patients were observed. The most that can be concluded from this part of the study is that sleep may be important in the pathogenesis of nocturnal bronchoconstriction in some patients, and that very short periods of sleep might be sufficient to produce these effects.

The authors of this complex study (Hetzel and Clark, 1979) concluded that sleep disruption is unlikely to be of value in the treatment of nocturnal asthma. However, they were unable to exclude a causal relationship between sleep and nocturnal bronchoconstriction.

Reinhardt and colleagues (1980), in contrast, were able to abolish nocturnal bronchoconstriction in seven asthmatic children by keeping them awake all night. However, their study was also inconclusive for it contained no details as to how wakefulness was assessed, nor is it clear how the children were prevented from sleeping at night.

It would be important to know, for example, whether they were given coffee to keep them awake, since this can act as a bronchodilator over and above any indirect effect through sleep deprivation (Salter, 1859; Rall, 1980; Becker et al, 1984).

### 3. Is nocturnal bronchoconstriction related to sleep stage?

Several groups have recorded electroencephalograms in sleeping asthmatics and noted the sleep stage when patients awoke with attacks of asthma. Ravenscroft and Hartman (1968) studied three asthmatics during 21 subject nights and found that 20 of the 37 asthmatic attacks occurred during REM sleep ( $P < 0.001$  on Chi-square test). However, this work was reported only in abstract form and these results were not confirmed in subsequent studies. In the largest of these studies, including 93 "asthmatic episodes" recorded in twelve patients on a total of 35 study nights, Kales and colleagues (1968) found that asthmatic attacks were randomly distributed throughout the stages of sleep in proportion to the amount of time spent in each sleep stage. The results of two smaller studies, one in asthmatic children (Kales et al, 1970) and the other in adults (Montplaisir et al, 1982), suggested that deep sleep (stages 3 and 4) may protect against asthmatic attacks.

However, the interpretation of all these studies is complicated by a number of factors. First, in each of these studies, the definition of an "asthmatic episode" was based on the patients' use of bronchodilator inhalers. In only one of the investigations

(Montplaisir et al, 1982) was bronchoconstriction documented by measurements of  $FEV_1$  and even in that study, a nocturnal attack was defined on the basis of symptoms.

Second, none of these investigators distinguished the effects of sleep stage on bronchoconstriction itself from possible sleep stage effects on arousal from asthmatic attacks. Most experiments in animals (Steriade and Hobson, 1976) and experiments in man using non-respiratory stimuli (Savin et al, 1973) have shown that it is more difficult to arouse patients from REM sleep than stage 2 sleep, but two recent experiments in man have shown that arousal with airway occlusion (Issa and Sullivan, 1983) and with hypercapnia (Berthon-Jones and Sullivan, 1984) is more rapid from REM sleep than NREM sleep. The effects of sleep stage on the arousal threshold to bronchoconstriction are unknown.

Finally, these investigations contained insufficient data to conclude that sleep stages 3 and 4 protect against asthmatic attacks, for slow wave sleep took up only a small proportion of total sleep time in the studies.

Montplaisir and colleagues (1982) noted that the most marked falls in  $FEV_1$ , and also the lowest  $SaO_2$  levels, usually occurred in the later hours of sleep, coinciding with the time when most REM sleep occurs, but as these authors pointed out, this does not prove any relationship between bronchoconstriction and sleep stage.

Interest in the possible effect of sleep stage on airway calibre has also been stimulated by observations in laboratory animals. Sullivan and colleagues (1979) monitored changes in tracheal smooth muscle tone during different sleep stages in four tracheostomised dogs by measuring the pressure in the water-filled cuff of their endotracheal tubes. During REM sleep, tracheal smooth muscle tone fluctuated markedly and erratically, as reflected by changes in cuff pressure as large as 90 cm water, although the changes were largely random with no consistent tendency to either bronchoconstriction or bronchodilatation. Partial blockade of the vagus nerves, by cooling exteriorised cervical vagal loops, decreased or abolished the fluctuations in tracheal smooth muscle tone during REM sleep at temperatures that did not abolish resting tone, demonstrating that changes in tone during REM sleep were related to variability in neural control of airway smooth muscle.

It is unclear, therefore, whether sleep causes bronchoconstriction in asthma. The results of previous studies involving sleep deprivation are difficult to interpret because of uncertainty that the patients were kept awake, whilst in other studies relating asthmatic attacks to EEG sleep stage the results have depended not only on bronchoconstriction but also on arousal from sleep, and on the eagerness of individual patients to use their inhalers during the night. In an attempt to overcome these problems, I performed three studies, which are described in the following chapters. The first involved measurements of peak expiratory flow in asthmatic patients kept awake all night. In this study, the patients were carefully



scrutinised throughout the night to ensure that they did not fall asleep, and wakefulness was confirmed electroencephalographically. In the second study, patients were woken briefly from known sleep stages and the degree of bronchoconstriction immediately assessed objectively by measurements of peak expiratory flow rate. In the third study, I attempted to determine whether changes in vagal tone are important in the pathogenesis of nocturnal bronchoconstriction, by studying the effect of the inhaled anticholinergic agent, ipratropium, on overnight changes in peak expiratory flow.

## Chapter 10

### EFFECT OF SLEEP DEPRIVATION ON NOCTURNAL BRONCHOCONSTRICTION

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In this study 12 asthmatic patients who reported nocturnal wheezing were kept awake all night to see whether this altered their nocturnal bronchoconstriction or their morning bronchial reactivity to histamine.

#### METHODS

##### Patients

Clinical details of the 12 asthmatic patients studied (9 men and 3 women, aged 22-58 yr) are given in table 7 (patients 1-12). All had documented nocturnal bronchoconstriction with peak expiratory flow rate (PEFR) recorded four times daily in the week prior to study showing an average circadian change (highest PEFR - lowest PEFR/highest PEFR) of 29% (range 10 - 68%). Eight had positive skin prick test responses to at least two common allergens and seven had a family history of atopy. Six were lifelong non-smokers, four (two atopic) were ex-smokers, and two (both atopic) smoked 10-15 cigarettes per day. All patients had been attending our clinic for at least one year but none had had an acute attack of asthma in the

TABLE 7

## CLINICAL DETAILS OF ASTHMATIC PATIENTS STUDIED IN SECTION IV

Patient No	Age (yr)	Sex	FEV <sub>1</sub> H	FEV <sub>1</sub> L	Diurnal variation in PEFR(%)	Skin tests	FH of atopy	Smoker	Regular treatment
1	23	M	4.2	2.0	27	Pos	Yes	No	S,C
2	54	M	3.5	1.8	37	Pos	Yes	No	S,B
3	63	M	2.2	1.3	31	Neg	No	No	S,B
4	18	F	3.3	0.9	68	Pos	Yes	Ex	S,B,C
5	35	F	3.6	1.3	11	Pos	No	No	S,B,T
6	21	F	3.9	1.5	21	Pos	Yes	Yes	S,B,T
7	20	M	4.4	2.1	10	Pos	Yes	No	S,C
8	24	M	4.6	3.6	10	Neg	No	No	S,C
9	26	M	4.0	2.3	42	Pos	Yes	Ex	S,B,I,P
10	57	M	2.7	1.2	25	Pos	Yes	Ex	S,B
11	57	M	2.7	1.3	31	Pos	No	Ex	S,P,T
12	58	M	2.1	1.4	31	Neg	No	No	S,B,P
13	31	F	3.8	1.3	39	Pos	Yes	No	S,B,D
14	37	F	3.0	1.5	ND	Pos	Yes	No	S,B,T
15	21	M	3.1	1.9	ND	Pos	Yes	No	S,B,C
16	46	M	2.8	1.4	13	Pos	Yes	Ex	S,B,C,I
17	51	M	2.2	1.3	21	Pos	Yes	Ex	S,B,I
18	34	M	4.4	1.5	ND	Neg	Yes	No	S,B
19	50	M	2.7	1.0	ND	Pos	No	Ex	S,C
20	59	M	2.4	1.6	ND	Neg	No	Ex	S,B,I,P,T
21	64	M	3.2	1.6	ND	Neg	No	No	S,B,P,T

M, male; F, female, FEV<sub>1</sub>, forced expiratory volume in one second; H, highest FEV<sub>1</sub> in last year recorded at clinic; L, lowest FEV<sub>1</sub> in last year; PEFR, peak expiratory flow rate; Pos, positive skin prick tests to at least two common allergens; Neg, negative skin prick tests; FH, family history; S, inhaled beta-2 agonist; B, inhaled corticosteroid; I, inhaled ipratropium; C, inhaled disodium cromoglycate; P, oral prednisolone 5-10 mg daily; T, oral theophylline; O, oral beta-2 agonist; ND, not determined.

six weeks before the study. All used beta<sub>2</sub> agonist inhalers and one an anticholinergic inhaler, nine inhaled corticosteroids, and four inhaled sodium cromoglycate. Three patients took 5-10 mg daily of oral prednisolone and five were taking oral theophyllines. The theophyllines were discontinued 24 hours before each study night and the beta<sub>2</sub> agonist and anticholinergic inhalers six hours before each study night. The corticosteroids and sodium cromoglycate were continued at an unchanged dose.

### **Procedure**

Each patient was studied on two occasions, an "awake night" and an "asleep night" 7-14 days apart, the order of the two nights being randomly determined.

On the "asleep night", which was preceded by a night of acclimatisation under the same conditions, each patient slept undisturbed in a quiet, darkened room. PEFR was recorded in the seated position before sleep at 10 pm, after sleep at 7 am, and also if the patient awoke during the night asking to use an inhaler. All PEFR measurements on each night were made by the same technician using the same instructions. Sleep was scored (Rechtschaffen and Kales, 1968) from an electroencephalogram, electrooculogram and electromyogram, as outlined in chapter 2.

On the "awake night" the patients played cards or board games and watched non-stimulating films; they were permitted to walk slowly around the sleep laboratory complex but were not allowed out of

doors, and such mild exertion was always less than 15 minutes a night. They were denied substances containing caffeine as these are bronchodilators (Fall, 1980; Becker et al, 1984). They were supervised constantly by two members of staff, who ensured that they did not sleep; and whenever they were seated or lying wakefulness was confirmed electroencephalographically. On the awake night, PEFr was recorded at 2-hourly intervals, again with the subjects seated. At 7 am after each study night bronchial reactivity to histamine was assessed (Chai et al, 1975) to see whether overnight wakefulness blunted bronchial reactivity.

Before each study the subjects performed a normal day's work and were instructed not to sleep. Venous blood was drawn at the beginning of each study; it contained very low concentrations of caffeine (less than 0.9 ug/ml) in all patients and detectable theophyllines in only five patients - in each case the theophylline level was < 3.3 ug/ml.

In the last four patients studied venous blood was sampled hourly throughout the night, both on the awake night and the asleep night, a venous catheter having been inserted at the elbow at the start of the study. The blood was collected into cold heparinised syringes and immediately spun in a refrigerated centrifuge. The plasma was then frozen at  $-70^{\circ}\text{C}$  for subsequent analysis for 11-hydroxycorticosteroid and catecholamine levels. On the awake night the four patients rested supine for 15 minutes prior to each blood sample. The plasma samples were transported in dry ice to the Department of Materia Medica, University of Glasgow, and there analysed radioenzymatically

(Da Prada and Zurcher, 1975) for 11-hydroxycorticosteroid and catecholamine levels under the supervision of Professor J L Reid.

The significance of differences was assessed by Student's t test for paired data or by analysis of variance and Duncan's multiple comparison test (Snedechor and Cochrane, 1980).

## RESULTS

### EEG sleep stage

On the awake night all patients remained awake throughout the night. On the asleep night the sleep period time averaged  $413 \pm 14$  (SEM) min, during which there were  $55 \pm 16$  min of wakefulness,  $21 \pm 4$  min of stage 1 sleep,  $172 \pm 11$  min of stage 2,  $43 \pm 5$  min of stage 3,  $56 \pm 9$  min of stage 4, and  $66 \pm 10$  min of REM sleep.

### Overnight bronchoconstriction

The results are shown in figs 21-23. Full details of the results from the individual studies are shown in fig 31 in the appendix.

Seven of the 12 patients did not use an inhaler on either night; three did so only on the sleep night (at 2.40, 4.00 and 5.30), and two used their inhalers on both nights (at 1.00 and 4.20 on the asleep night and at 3.00 and 6.00 respectively on the awake night). Thus no patient used his inhaler earlier on the awake night than on the asleep night. In the seven patients who did not use inhalers, the overnight changes in PEFr were compared on the basis of the 7 am

values. In the other five patients, the pre-inhaler PEFR on the asleep night was compared with the nearest time-matched PEFR on the awake night (fig 21).

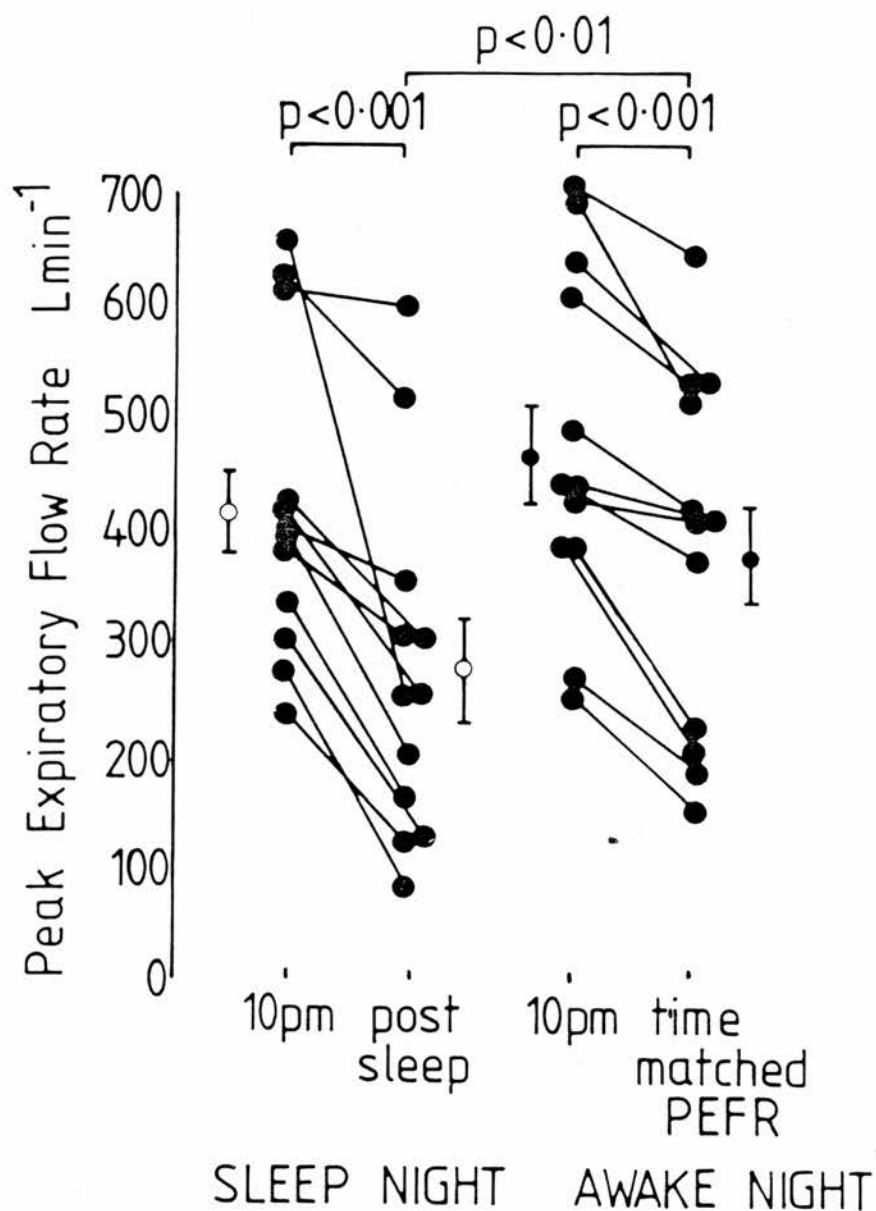
All patients showed overnight bronchoconstriction both on the asleep night and on the awake night (fig 21). The PEFR fell to lower values on the asleep night ( $270 \pm 46$  l/min) than on the awake night ( $371 \pm 43$  l/min;  $p < 0.01$ ). The overnight fall in PEFR was significantly greater on the asleep night than on the awake night, both in terms of absolute fall in PEFR (asleep night  $148 \pm 28$ , awake night  $84 \pm 13$  l/min;  $p < 0.02$ ) and as a percentage fall in PEFR (asleep night  $38 \pm 6\%$ , awake night  $20 \pm 4\%$ ;  $p < 0.01$ ). PEFR at 10 pm on the awake night ( $465 \pm 43$  l/min) tended to be higher than on the asleep night ( $418 \pm 40$  l/min), but this was not a significant difference ( $0.1 > p > 0.05$ ).

#### Plasma hormone levels

In the four patients in whom venous blood was sampled there was no consistent change in 11-hydroxycorticosteroid levels between the awake and asleep night. In all four subjects, plasma adrenaline was higher throughout the asleep night than on the awake night, and there was a trend for plasma noradrenaline also to be higher on the asleep night (fig 22).

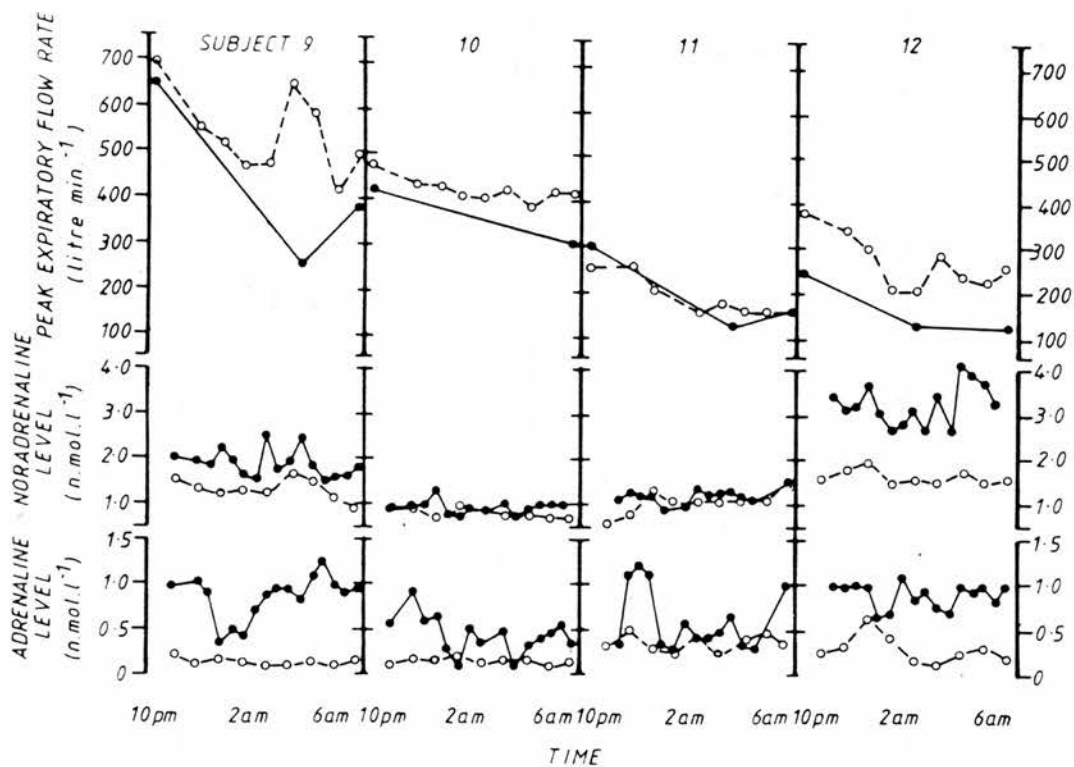
#### Bronchial reactivity to histamine

In 11 patients bronchial reactivity to histamine was assessed at 7 am after both the asleep night and the awake night. The 12th patient was excluded from histamine challenge because his morning value of

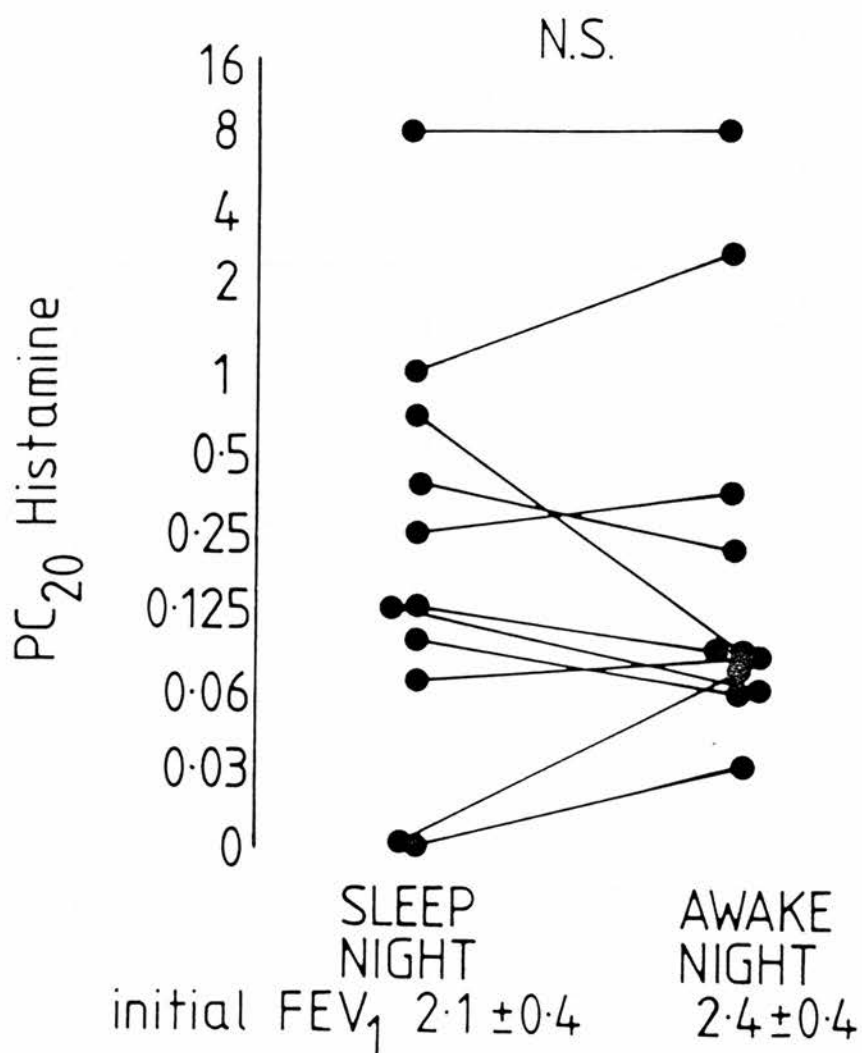


**Fig 21** Peak expiratory flow rates at night and in the morning in 12 patients on a night when they slept (left) and a night when they were kept awake (right). The error bars shown are SEM's.





**Fig 22** Peak expiratory flow rates and plasma noradrenaline and adrenaline levels in 4 asthmatic patients on a night when they slept (solid line) and a night when they were kept awake (broken lines).



**Fig 23** The concentration of histamine required to reduce forced expiratory volume in 1 second (FEV<sub>1</sub>) by 20% (PC<sub>20</sub>) in 11 asthmatic patients after a night when they slept (left) and a night when they were kept awake (right).

FEV<sub>1</sub> was less than 1 litre (Pepys and Davies, 1977) on both mornings. There was no difference between the awake night and the asleep night in the bronchial reactivity to histamine, as assessed by the concentration of histamine which reduced FEV<sub>1</sub> by 20% (fig 23), even though the pre-histamine FEV<sub>1</sub> was lower after the asleep night.

### DISCUSSION

This study shows that patients with nocturnal asthma develop bronchoconstriction at night even if they are kept awake. However, the patients in this study showed greater falls in peak flow on the night when they slept. Furthermore, five patients had to use their bronchodilator aerosols during the asleep night but only two during the awake night, and both of these used the inhaler later on the awake night than on the asleep night. Thus the study shows that sleep, while not essential for nocturnal bronchoconstriction, has a role in airway narrowing at night. In this study approximately half of the overnight fall in peak flow was prevented by keeping the patients awake. There was no change in bronchial reactivity after overnight wakefulness.

This is the first study of the effect of sleep deprivation on nocturnal asthma which has documented wakefulness by electroencephalography and which has excluded the ingestion of caffeine (a bronchodilator) which would confuse the results. Our observations, therefore, extend those of Hetzel and Clark (1979) who attempted to keep asthmatics awake until the early morning and found

that most, but not all, showed their usual degree of nocturnal bronchoconstriction before going to sleep. However, electroencephalograms were not recorded in that study as discussed in chapter 9. Conflicting evidence came from the study of Reinhardt and colleagues (1980), who found that nocturnal bronchoconstriction in asthmatic children was abolished by sleep deprivation, although it is not clear how the children in that study were kept awake.

The finding in the current study that sleep contributes to the pathogenesis of nocturnal bronchoconstriction in asthma is supported by studies in asthmatic shift workers (Clark and Hetzel, 1977; Connolly, 1979) in whom the time of sleep determined the time of the fall in peak flow, irrespective of the time of day.

Why were higher peak flow rates obtained after the awake night? Other differences between the awake night and the asleep night were minimised but cannot totally be excluded as factors. Both nights were spent in the same rooms at the same temperature (Chen and Chai, 1982) and precautions were taken to keep the house dust mite count low (Platts-Mills et al, 1982). It was not feasible for the patients to be lying down throughout the night they were kept awake, as we would have been unable to keep these volunteer patients fully awake as defined electroencephalographically. Posture effects are unlikely to explain the differences in peak flow, however, since nocturnal bronchoconstriction is unchanged whether patients are ambulant by day or are kept lying in bed throughout the 24 hour period (Clark and Hetzel, 1977).

There was a trend for PEF<sub>R</sub> at 10 pm to be higher on the awake night than on the asleep night. This trend is difficult to explain. It was necessary for the patients to know in advance which night they were going to be awake so that they could arrange work schedules; but if they had had a nap (which each denied) before coming in on the awake night the PEF<sub>R</sub> would be expected to have been lower at the start of that night, whereas the trend was towards the reverse. This non-significant trend seems unlikely to be the reason for the significantly smaller falls in both absolute and percentage PEF<sub>R</sub> on the awake night.

It seems more likely that sleep itself influences nocturnal asthma. Such an effect of sleep could be either direct or indirect.

Direct effects of sleep on breathing, such as changes in breathing pattern (Chapters 4, 6) and ventilatory control (Douglas et al, 1982b, c), are transient and on arousal return to the patterns of those found in wakefulness. The effect of sleep on nocturnal asthma is clearly different from these effects as nocturnal bronchoconstriction persists after awakening.

Indirect mechanisms might include the role of sleep in controlling circadian rhythms of hormones (Soutar et al, 1977; Barnes et al, 1980), body temperature (Chen and Chai, 1982), autonomic nervous activity (Baust and Bohnert, 1969; Gaultier et al, 1977) or other factors. The sleep-wake cycle is important in synchronising

circadian rhythms, and disruption of this cycle by enforced overnight wakefulness would alter such rhythms. It has been suggested that nocturnal asthma results from overnight falls in circulating adrenaline (Soutar et al, 1977; Barnes et al, 1980) and the results of our study could be explained were circadian changes in adrenaline concentrations altered by overnight wakefulness. Previous studies in normal subjects have found no consistent changes in circulating catecholamines during overnight wakefulness (Prinz et al, 1984), and the hormone results in the four subjects in this study similarly provide no evidence that the effect of sleep on nocturnal asthma is mediated through either catecholamine or cortisol levels. In fact, the catecholamines tended to be lower when the asthmatics were awake. This study does not address the issue of whether the non-sleep determined component of nocturnal asthma is caused by circadian changes in catecholamines (Soutar et al, 1977; Barnes et al, 1980) or circulating corticosteroids (Soutar et al, 1975).

In order to clarify the effects of sleep on bronchoconstriction in asthma, another study was performed to determine whether changes in peak flow are related to individual sleep stages. This study is described in the next chapter.

## Chapter 11

### **THE RELATIONSHIP BETWEEN NOCTURNAL BRONCHOCONSTRICTION AND EEG SLEEP STAGE**

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In this study, 8 adult asthmatics who complained of nocturnal wheeze and age-matched control subjects were awakened at different times during the night, from known EEG sleep stages, and their FEV<sub>1</sub> and PEF<sub>R</sub> measured immediately. The protocol was designed to determine whether there was any difference in airway calibre between REM and NREM sleep in adult asthmatics and to compare any such difference with underlying circadian changes.

#### **METHODS**

##### **Subjects**

Eight patients with asthma (5 male, 3 female) were studied, including four who had also taken part in the sleep deprivation study (Chapter 10) the interval between the two studies for each patient being at least 3 months. Their clinical details are given in table 7 (patients 2, 4, 7, 9, 11, 13-15). Their mean age was 30 yr (range 15 - 54 yr) and all were within 15% of their ideal body weight

(Documenta Geigy, 1970). All had reversible airways obstruction with at least one  $FEV_1$  during the preceding year that was within 1.5 standard deviations of predicted. Seven had positive skin prick tests to *D. pteronyssinus* and/or grass pollens. All complained of nocturnal wheeze and had documented "morning dips" in peak expiratory flow rate (PEFR). None had had an acute attack of asthma in the six weeks prior to the study. Two took regular inhaled sodium cromoglycate and two oral prednisolone (5 and 10 mg/daily). All used  $\beta_2$  sympathomimetic agents but these were withheld for six hours before the study. Each patient was matched for age and sex with a healthy subject with no history of respiratory disease who was studied on the same night as the patient.

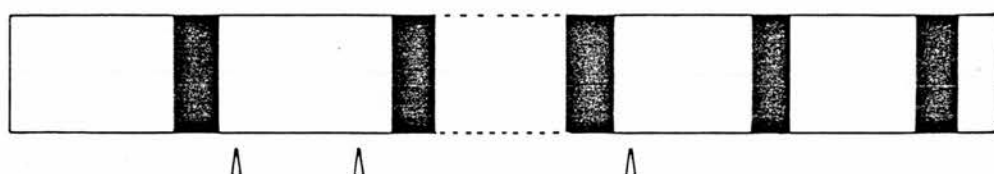
### **Protocol**

Each subject slept for three consecutive nights in the sleep laboratory, the first serving as an acclimatisation night. On each night they were awoken from sleep on three occasions and immediately asked to perform forced expiratory manoeuvres so that PEFR and  $FEV_1$  could be measured. The timing of their awakenings on the second and third nights was designed to differentiate temporal from sleep stage related changes in airway calibre (fig 24).

On one night (night A) the patients were awoken 10 minutes after the end of the first REM period and again 60 minutes later, before the start of the next REM period (fig 24), i.e. both awakenings were from NREM sleep, without intervening REM.



NIGHT A



NIGHT B



□ NREM SLEEP

■ REM SLEEP

11pm 12mn 1am 2am 3am 4am 5am 6am 7am

**Fig 24** Schematic diagram of times of waking on second and third nights. Broken lines indicate second randomisation, in which wakenings from REM and NREM (non-REM) sleep were random.

On the other night (night B) the patient was awoken 60 minutes after sleep onset, prior to the first REM period, and 5-7 minutes after the start of (i.e. during) the second REM period. Thus there was a REM period between the two awakenings and, furthermore, the second awakening was made during a REM period (fig 24). The order of night A and night B was randomised so that half the patients did each night first.

The third awakening on both nights was designed to give "time-matched" measurements of airway calibre in REM and NREM sleep. Thus, on one night, the third awakening was made from the first REM period after 4 am, and on the other night it was made during the first NREM period after 4 am. The order of these nights was randomised independently of the night A/night B randomisation (fig 24).

On both nights measurements of  $FEV_1$ , forced vital capacity and PEFr were also made at: 9.30 pm; at 11 pm just before lights out; immediately on final awakening in the morning; and finally one hour thereafter. On each of these occasions and following imposed awakenings, the PEFr was measured first with the subject supine, then  $FEV_1$  was measured with the subject sitting on the bed and finally both PEFr and  $FEV_1$  were measured while the subject was standing. All measurements were made in duplicate except for the standing  $FEV_1$  which was measured in triplicate and on each occasion the highest value was taken.

Each patient slept in a quiet, darkened room on each night of the study and EEG sleep stage was determined by the methods previously described (Rechtschaffen and Kales, 1968).

The actual measurements of  $FEV_1$  and PEF<sub>R</sub> were made by a nurse who was trained in these measurements and who was blind to the protocol and who did not know the EEG sleep stage from which the patient had been woken. The timings of the awakenings on each night were decided by Dr Shapiro since he had greater expertise in the analysis of EEG sleep stages than I. This is the only study in the thesis in which I did not collect the majority of the data myself. However, I did initiate the study and I designed the study with the assistance of Dr Shapiro. I also recruited the patients, and I helped to analyse and interpret the results with the assistance of Dr G Raab (Department of Medical Statistics, University of Edinburgh) who performed the multiple regression analysis (see below).

Results are quoted as means  $\pm$  standard error of the mean. Statistical analysis was by Student's "t" test for paired comparisons. The Wilcoxon signed rank test was used for the pooled information depicted in figure 25. All the data obtained when the subjects were awakened were analysed by multiple regression methods (Baker and Nelder, 1978) to enable the effects of sleep stage and time to be separated.

## RESULTS

### Sleep

Despite the three deliberate awakenings, the subjects spent most of the time asleep, and there was a tendency for the asthmatics to sleep less well than the control subjects. Total sleep time averaged 427 min in the normal subjects, compared with 398 min in the asthmatic patients, but this was not a significant difference. The normal subjects spent less time awake (mean 44 min) than did the asthmatics (64 min;  $p < 0.05$ ) and they also spent more time in stage 2 sleep (234 min) than did the asthmatics (201 min;  $p < 0.05$ ). The mean durations of stage 1 sleep (normal, 29: asthma, 36 min) stage 3 sleep (normal, 27: asthma, 23 min), stage 4 sleep (normal, 50: asthma, 51 min) and REM sleep (normal, 87: asthma, 87 min) were each similar in the two groups in this study.

### Forced expiratory manoeuvres

The results are in figs 25 and 26. Detailed results from each study are shown in figs 32a-d in the appendix.

### Normal subjects

In the eight normal subjects there was no significant bronchoconstriction overnight, eg PEFR supine was  $413 \pm 38$  l/min pre sleep and  $400 \pm 40$  l/min at each individual's lowest PEFR during the night. There was also no difference in time-matched REM and NREM measures in the normal subjects, eg FEV<sub>1</sub> standing was  $3.5 \pm 0.4$  l and  $3.5 \pm 0.4$  l on awakening from REM and NREM sleep respectively.

### Asthmatic patients

Every patient bronchoconstricted overnight, eg PEF<sub>R</sub> supine was  $410 \pm 50$  l/min pre -sleep and  $186 \pm 49$  l/min at the lowest level overnight.

One patient (patient 2; fig 32, appendix) used a bronchodilator inhaler after the first waking on night B. The subsequent data from that night has been excluded from the analysis.

#### (i) Changes in PEF<sub>R</sub> and FEV<sub>1</sub> with and without intervening REM sleep:

All measurements of forced expiratory flow rate (PEF<sub>R</sub> both lying and standing, FEV<sub>1</sub> both sitting and standing) decreased significantly more (range of p values 0.04 - 0.02; table 8) when there had been intervening REM sleep periods (night B) than when there was no intervening REM sleep (night A). However, the intervals containing REM sleep were significantly longer ( $190 \pm 26$  min) than the intervals without any REM sleep ( $61 \pm 3$  min). Thus this comparison cannot fully distinguish effects of sleep stage from those due to time.

#### (ii) PEF<sub>R</sub> and FEV<sub>1</sub> during "time-matched" awakenings from REM and NREM sleep:

To examine predicted sleep stage effects while reducing any temporal effects, we compared the measurements of FEV<sub>1</sub> and PEF<sub>R</sub> made during the first NREM period after 4 am with those made during the first REM period after 4 am ("time-matched" measurements). There was no significant difference between the measurements made during awakenings from REM sleep compared with those during awakenings from NREM sleep,

**TABLE 8**

**MEAN CHANGE IN PEFR AND FEV<sub>1</sub> WITH AND  
WITHOUT INTERVENING REM SLEEP**

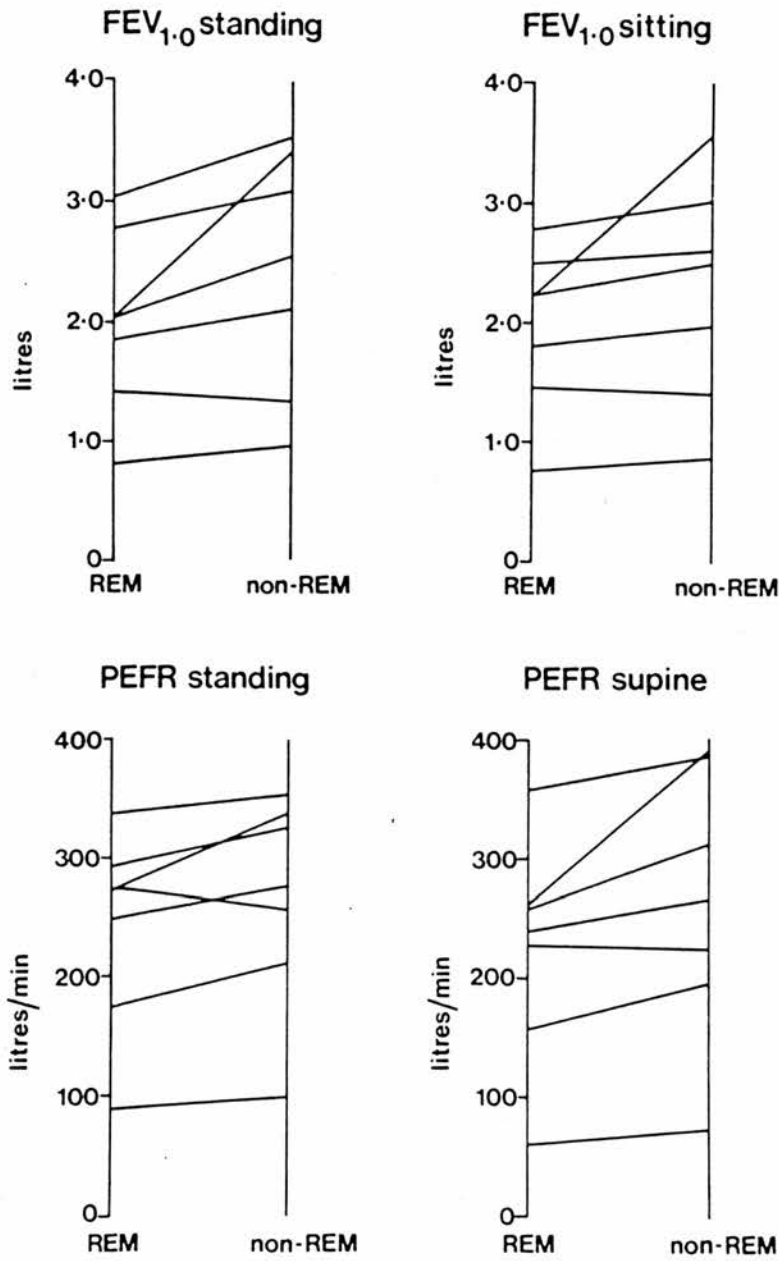
	Without intervening REM sleep (night A; n = 7)	With intervening REM sleep (night B; n = 7)
Duration of interval between measurements (min)	61	190
PEFR lying (l/min)	-9	-74
PEFR standing (l/min)	-39	-120
FEV <sub>1</sub> sitting (l)	-0.03	-0.4
FEV <sub>1</sub> standing (l)	-0.02	-0.7

but for all parameters of forced expiratory flow (PEFR lying and standing,  $FEV_1$  sitting and standing) the REM measurements tended to be lower than the NREM measurements.

However, this analysis was complicated by a number of factors, viz: (i) patient 2 (fig 32) used his inhaler on one night (see above) and on the other night did not enter REM sleep after 4 am; (ii) in patient 3 (fig 32), the second waking on night B was after 4 am; and (iii) on night B, patient 6 did not fall asleep after 4 am.

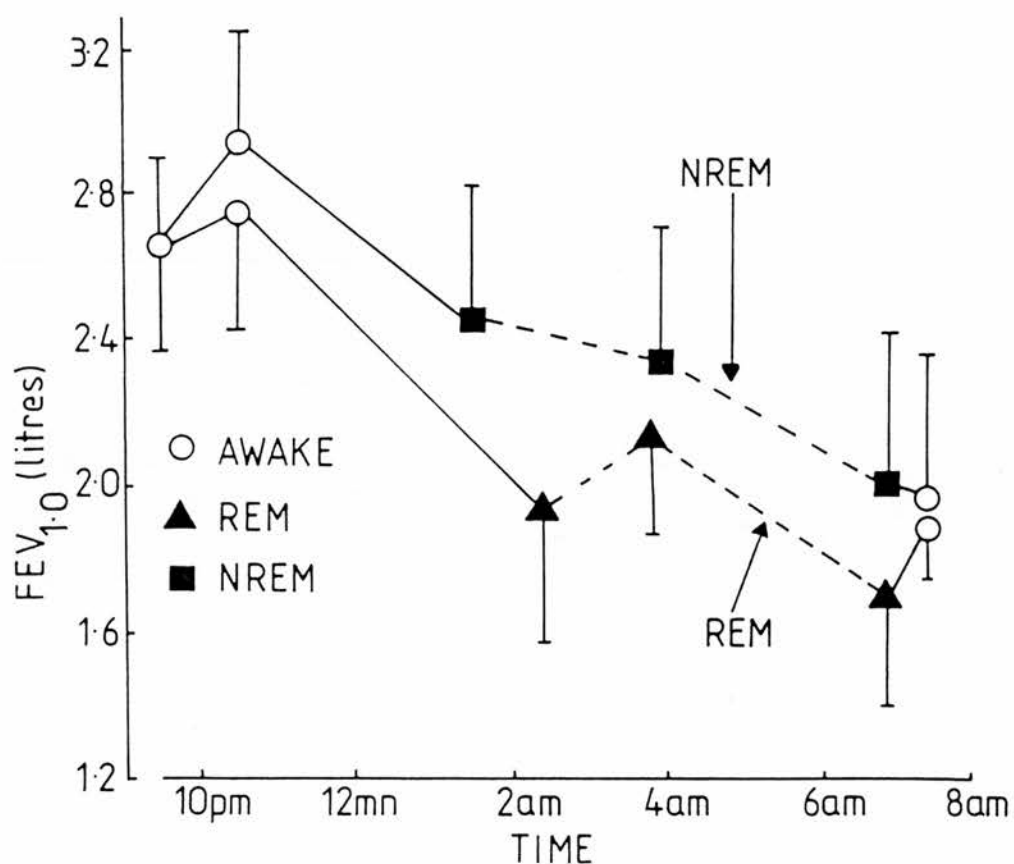
To obtain more data for this analysis, covering a wider time period, we included "time-matched" measurements made at two other times during the night and, for this analysis only, we also included results from the acclimatisation nights whenever this enabled a "time-matched" comparison to be made that would not have been possible otherwise. Thus: (1) In five patients  $FEV_1$  and PEFR measurements on final awakening were made from NREM sleep on one night and from REM sleep on the other night: (2) The second awakening on night A (from NREM sleep) was compared with the second awakening on night B (from REM sleep) in each patient. Taking all 19 "time-matched" measurements (seven at the second awakening on each night, seven at 4 am and five on final awakening), the REM measurements were on average  $21 \pm 8$  (range -4 to +69) minutes later than the matched NREM measurements.

Averaging the two or three "time-matched" measures for each subject (and thus avoiding bias towards the subjects with more measurements),



**Fig 25** Peak expiratory flow rate and forced expiratory volume in 1 second in postures indicated after patients were woken from REM and NREM (non-REM) sleep. Each line represents average of 3 time-matched comparisons (5 patients) or 2 time-matched awakenings (2 patients). For all measures,  $p < 0.05$ .





**Fig 26** Forced expiratory volume in 1 second (FEV<sub>1</sub>) measured standing after wakening from REM or NREM (non-REM) sleep at times indicated: values are means  $\pm$  SEM in 7 patients using data from both night A and night B. Solid lines join data obtained in the subjects on the same night: broken lines indicate when data were from different nights owing to the two separate randomisation procedures.

all measurements of forced expiration after awakenings from REM sleep were significantly lower ( $p < 0.05$ ) than the measurements following "time-matched" NREM awakenings (fig 25). The data obtained from this "time-matched" comparison of wakenings from REM and NREM sleep were plotted against the time of night (fig 26). The overall decrease in  $FEV_1$  overnight was much greater than the difference in  $FEV_1$  between REM and NREM sleep.

(iii) Regression analysis:

Since the above "time-matched" awakenings for REM sleep were on average later than those from NREM sleep, they could not fully differentiate sleep effects from temporal effects. Furthermore, the above analysis of "time-matched" values did not use all the data collected to separate the effects on forced expiration of time of night from those due to sleep stage. This was achieved by fitting a regression model to all the data obtained in each patient, using the statistical package GLIM (Baker and Nelder, 1978). In the final model (table 9) for all four measurements of forced expiration ( $FEV_1$  and PEFr each in two postures) the most important influence was that of time ( $p < 0.01$ ). Taken over the whole night, the effect of REM sleep was significant for one of the respiratory measures (PEFR lying,  $p < 0.05$ ) but not significant ( $0.1 > p > 0.05$ ) for the other measures. However, when a model was fitted which allowed the influence of REM sleep to decline with time of night, this gave a significantly better fit for all four expiratory manoeuvres ( $p < 0.05$ ). The effect of REM sleep was greatest early in the night and declined towards morning for all forced expiratory measurements.

TABLE 9

## EFFECT OF RAPID EYE MOVEMENT SLEEP ON BRONCHOCONSTRICTION

Fitted values of the variables in the linear equation derived from all the data from the 8 asthmatics:

$$Y = P_i - tS_i - D_{REM} + (t-2)S_{REM}$$

where

$Y$  =  $FEV_1$  (or  $PEFR$ ) in each posture

$P_i$  =  $FEV_1$  (or  $PEFR$ ) in NREM sleep at midnight in the  $i$ th patient

$t$  = time after midnight (hours)

$S_i$  = slope of  $FEV_1$  (or  $PEFR$ ) decline with time in the  $i$ th patient

$D_{REM}$  = decrease in  $FEV_1$  (or  $PEFR$ ) due to REM sleep at 2 am

$S_{REM}$  = change in effect of REM sleep on  $FEV_1$  (or  $PEFR$ ) with time

Y	Mean $P_i$ (Range)	Mean $S_i$ (Range)	$D_{REM}$	$S_{REM}$
PEFR	1/min	1/min/hr	1/min	1/min/hr
standing	362 (200-534)	14 (-2 - 50)	82	19
sitting	322 (162-454)	13 (2 - 38)	74	21
$FEV_1$	l	1/hr	l	1/hr
standing	2.72 (1.61-3.72)	0.11 (0.02-0.28)	0.46	0.12
sitting	2.58 (1.50-3.54)	0.10 (0.01-0.24)	0.39	0.10

## DISCUSSION

This study suggests that nocturnal bronchoconstriction in adult asthmatics may be associated with rapid eye movement sleep, but that there is also a major effect of time.

In Chapter 10, asthmatic patients were found to have smaller overnight falls in peak expiratory flow when they were kept awake all night than on nights when they slept. However, it was not clear whether this was due to disruption of the sleep-wake cycle, with its attendant effects on other circadian rhythms which might affect airway calibre, or to loss of time in one or more EEG sleep stages. The results of the present study extend those observations by establishing that the REM stage of sleep may be associated with bronchoconstriction independent of temporal effects. However, this REM effect was relatively small compared with the overall nocturnal bronchoconstriction, and was only significant in the early part of the night.

The lower flow rates found after awakening from REM sleep could be explained by impaired expiratory muscle function on wakening from REM, which is a sleep stage characterised by voluntary muscle hypotonia. However, the subjects were fully awake at the time of performing the expiratory manoeuvres with normal submental electromyogram tone. Further, the difference in forced expiratory flow rates was seen in each of the four sequential types of forced expiratory flow manoeuvres, and thus there was no evidence that the

effect was transient following awakening. Other studies of the performance of voluntary tasks on wakening from different sleep stages suggest that the worst performance occurs on wakening from stages 3 and 4 sleep, with no significant difference between stage 2 sleep - from which most of the NREM awakenings were made - and REM sleep (Wilkinson and Stretton, 1971). Further, the normal controls would be expected to show such a performance effect and they did not.

Thus we conclude that the significant effects of REM sleep in asthmatic patients on measurements of forced expiration reflect alterations in airway calibre. Asthmatics respond more than normal subjects to a wide variety of bronchoconstricting influences and this study suggests that REM sleep is another such stimulus.

REM sleep could either cause bronchoconstriction by a direct "on-off" effect or by producing a lasting effect which persists after the REM period has finished. The results from the modelling procedure and from the "time-matched" comparison both suggest that REM sleep has a direct effect on asthmatic airway calibre, but whether REM sleep has a persisting effect on airway tone is unclear. It is possible that the effect of REM sleep was underestimated in this study since the overnight decline may have resulted partially from an accumulative effect of REM sleep periods throughout the night. However, a decline in airway calibre was also observed between the awakenings without intervening REM sleep, suggesting that there is a time effect independent of the REM sleep effect.

The results of this study - suggesting that REM sleep causes bronchoconstriction - require confirmation as we studied relatively few subjects and by awakening them necessarily interrupted the variable under study, ie REM sleep. There have been no satisfactory measurements of bronchomotor tone in sleeping asthmatics (see Chapter 2), perhaps because oesophageal intubation is required for conventional measurement, and patients with nocturnal asthma sleep poorly (Chapter 6) even without such instrumentation. One study (Kales et al, 1970) used a tape-recording of breath sounds to try to detect bronchoconstriction, and found no relationship between REM sleep and bronchoconstriction in asthmatic children, but as ventilation is on average lower in REM sleep than NREM sleep (Douglas et al, 1982a; Stradling et al, 1985), wheeze might even decrease in REM despite bronchoconstriction. Nevertheless, the data presented above does suggest that REM sleep may be associated with bronchoconstriction.

The mechanism of bronchoconstriction in REM sleep requires elucidation. In dogs, the variability in bronchial smooth muscle tone during REM sleep can be abolished by cooling the vagus nerve (Sullivan et al, 1979). I therefore studied the effects of inhaled anticholinergic agents on nocturnal bronchoconstriction. These studies are described in the next chapter.

## Chapter 12

### **THE EFFECT OF AIRWAY VAGAL BLOCKADE ON NOCTURNAL BRONCHOCONSTRICTION**

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In the foregoing study, REM sleep was shown to be significantly associated with bronchoconstriction in asthma. Since REM-related fluctuations in airway calibre in dogs can be abolished by cooling the vagus nerves (Sullivan et al, 1979), and because of evidence that vagal activity increases at night both in cats (Baust and Bohnert, 1977) and human subjects (Gaultier et al, 1977; Postma et al, 1985), I attempted to study the effects of vagal blockade on nocturnal bronchoconstriction in patients with asthma, using the inhaled atropine-like drug ipratropium bromide.

#### METHODS

##### Patients

The asthmatic patients (8 men, 2 women) were aged 21 - 51 (mean 39.8) years (table 7; patients 2, 3, 7, 11, 16 and 21). None had had an acute exacerbation of asthma for at least six weeks. All complained of nocturnal wheeze, with a mean circadian change in PEFR (measured

four times daily for 5 - 7 days as an out-patient in six) averaging 22 percent (range 13 - 42 percent) of the highest daily value. All had reversible airways obstruction with a documented increase in FEV<sub>1</sub> of more than 20 percent after inhalation of bronchodilators. Seven had positive skin prick tests to at least two common allergens and seven had a family history of atopy. Three patients took a regular dose of prednisolone 5-10 mg daily, eight patients took inhaled corticosteroids regularly and two patients used inhaled sodium cromoglycate regularly. These were continued during the study, each at an unchanged dose, but oral theophyllines (used by three patients), oral salbutamol (two patients) and inhaled ipratropium bromide (two patients) were withdrawn 24 hours before the study. All patients used inhaled betasympathomimetic agents and these were withdrawn six hours before the study.

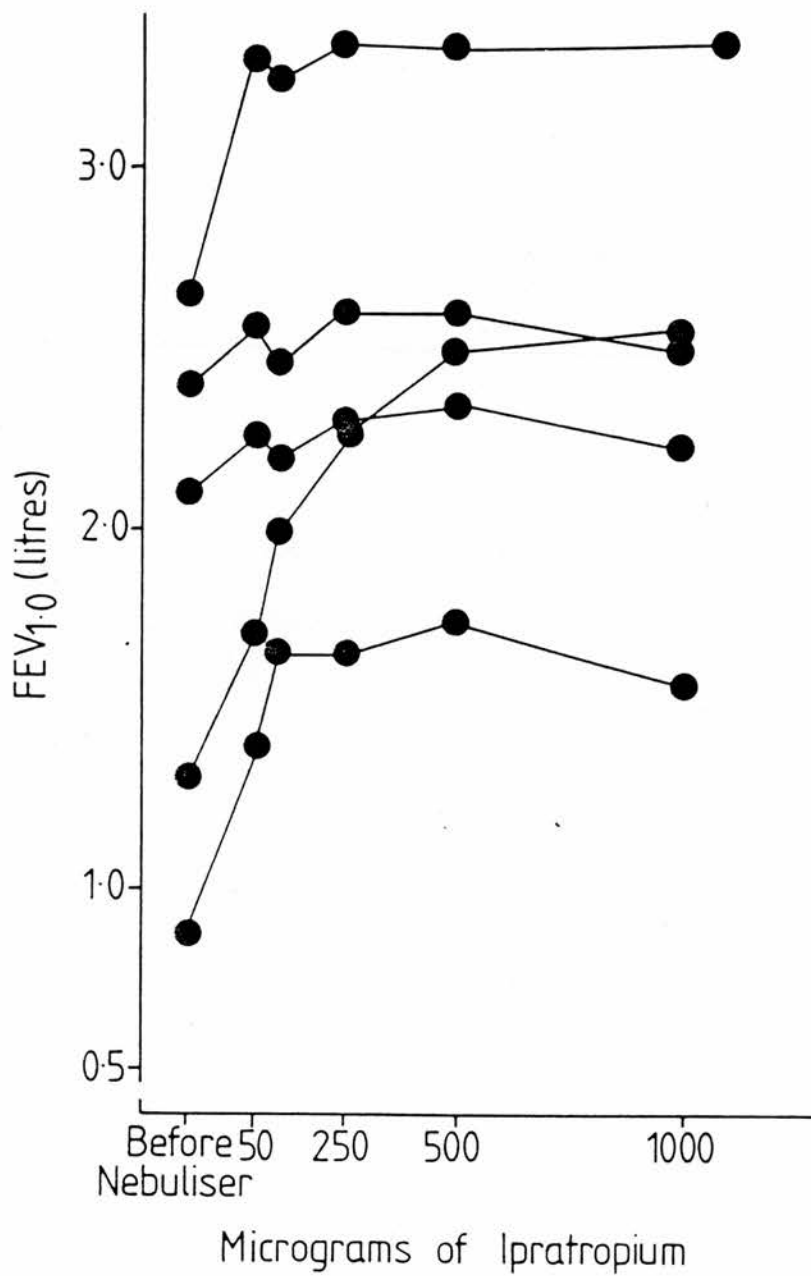
#### Dose response to ipratropium

One week prior to the night time study, a cumulative dose response curve to nebulised ipratropium was performed mid-morning in five of the patients, measuring FEV<sub>1</sub> after 50, 250, 500 and 1,000 ug of ipratropium. 250-500 ug produced maximal bronchodilatation (fig 27). The dose of ipratropium chosen for the study was 1 mg.

#### Protocol

The patients were studied on three consecutive nights, the first for acclimatisation. On the second and third nights they received either nebulised ipratropium (1 mg) or nebulised normal saline in random order, double-blind (fig 28).





**Fig 27** Effect of inhaled ipratropium on forced expiratory volume in 1 second in 5 patients with asthma: cumulative dose-response curve.

They arrived in the laboratory at 9.30 pm. At 10 pm, their peak expiratory flow was measured and the nebulised solution (either placebo or ipratropium) was administered. Ninety minutes later the peak flow was re-measured. They were allowed to sleep, but were wakened at 2 am when a peak flow rate was recorded and a further nebulisation of the same solution given. The patients were wakened again at 6 am, their peak flows were measured, and then, on both nights, they were given nebulised ipratropium 1 mg. After a further 90 minutes, the peak flow was measured again. Finally, on both nights, each patient received 5 mg of terbutaline by nebulisation and the peak flow was recorded 30 minutes later (fig 28).

At 10 pm, 11.30 pm, 2 am and 6 am, the pulse rate was measured during wakefulness before the peak flow measurements and before the administration of the nebulised solutions.

In six subjects, electroencephalographic sleep stage was recorded throughout the night as described in Chapter 2. Owing to technical problems, however, complete sleep data for both nights was recorded in only four subjects.

**Additional study to determine the effect of nocturnal ipratropium on the response to methacholine challenge at 6 am**

To determine whether ipratropium (1 mg) administered at 10 pm and 2 am blocked pulmonary cholinergic receptors throughout the night, four of the ten patients were restudied on a further two nights. On one

night they received 1 mg ipratropium at 10 pm and 2 am, and the on the other night they received nebulised saline at these times, double-blind and in random order as in the main study, but at 6 am, instead of receiving an ipratropium inhalation, they underwent a standard methacholine challenge (Chai et al, 1975). On each night, the concentration of methacholine which produced a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) was determined.

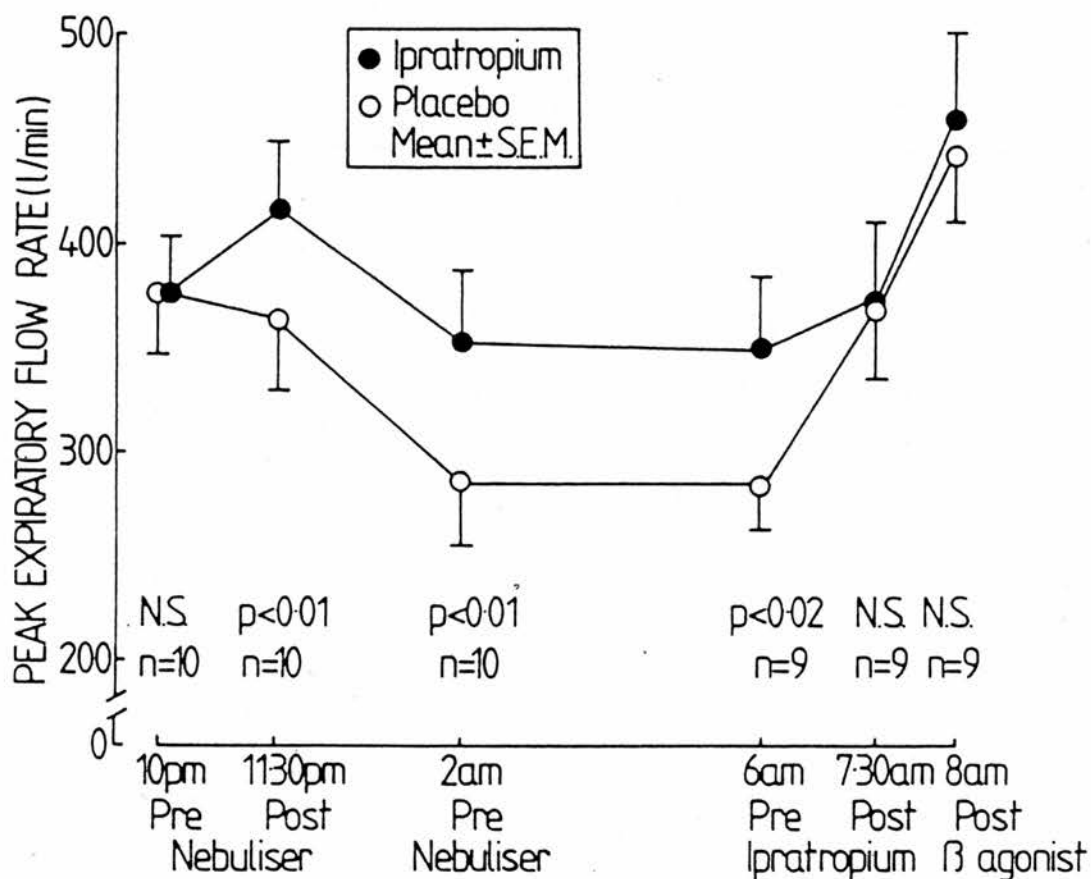
Differences were assessed by the paired "t" test.

## RESULTS

### Requests to use additional bronchodilators

One patient woke between 1 am and 2 am on both study nights and asked to use a bronchodilator. On each occasion, he was given the test nebuliser solution (either placebo or ipratropium) but in neither instance did he feel that this was sufficient to control his symptoms. He became anxious and requested that no further measurements be made. He was given nebulised terbutaline (5 mg) with relief of symptoms, and eventually returned to sleep. No measurements were made in this patient after 2 am, but measurements up to and including the 2 am (pre-terbutaline) measurement are included in the peak flow results below. When the code was broken, his peak flow at 2 am was found to be 220 l/min on the ipratropium night and 150 l/min on the placebo night.

None of the other seven patients requested to use additional



**Fig 28** Overnight change in peak expiratory flow rates in asthmatic patients on a night when they inhaled ipratropium (closed circles) and a night when they inhaled placebo (open circles). Ipratropium or placebo was administered at 10 pm, 2 am and 6 am. At 7.30 am, the patients received inhaled terbutaline.

bronchodilators on either night.

#### Effect of ipratropium on peak expiratory flow

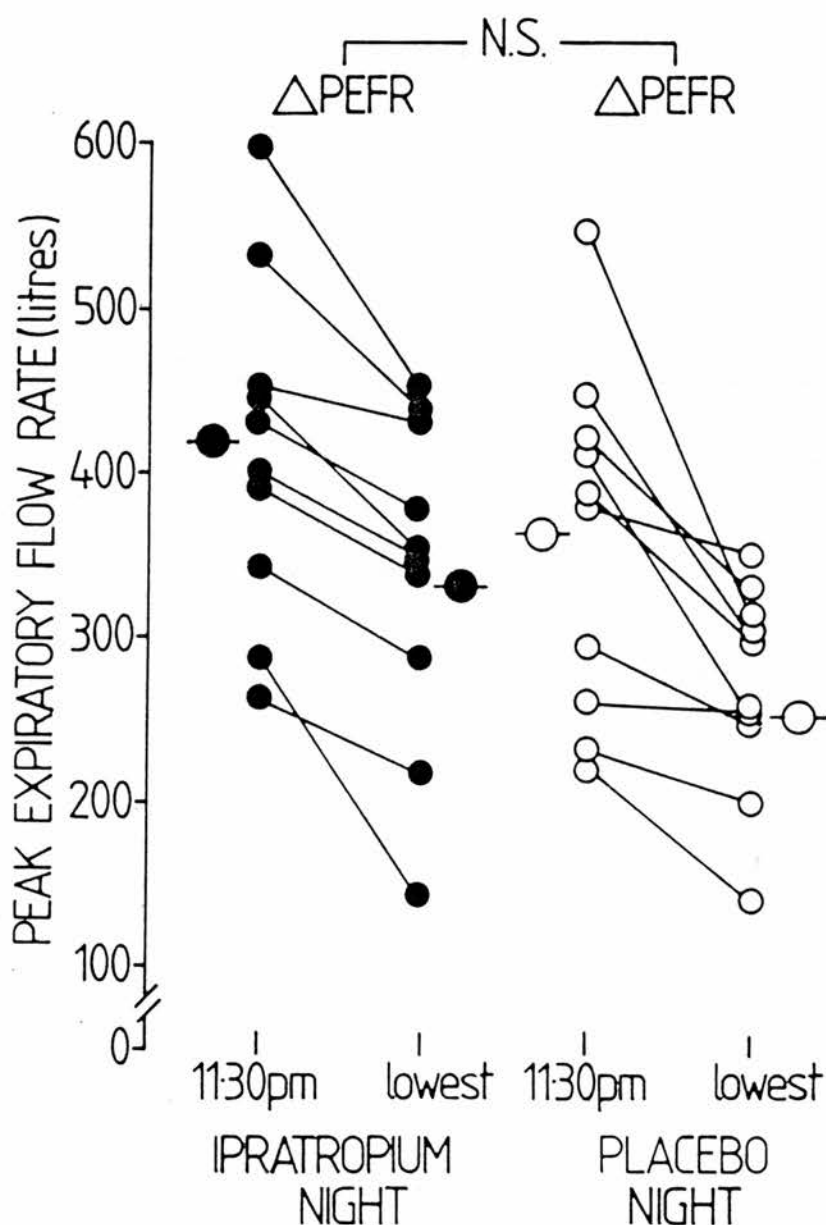
The PEFR at 10 pm was similar on the placebo night ( $376 \pm 29$  l/min) and ipratropium night ( $376 \pm 31$  l/min; NS; fig 28). Following placebo there was no change in PEFR ( $363 \pm 33$  l/min; NS; fig 28), but the PEFR did rise after ipratropium ( $415 \pm 33$  l/min;  $p < 0.02$ ; fig 28). This bronchodilating effect of ipratropium persisted, the PEFR measurements at 2 am and 6 am also being higher ( $p < 0.01$  and  $< 0.02$  respectively) on the ipratropium night than on the placebo night (fig 28).

#### Effect of ipratropium on the overnight fall in peak expiratory flow

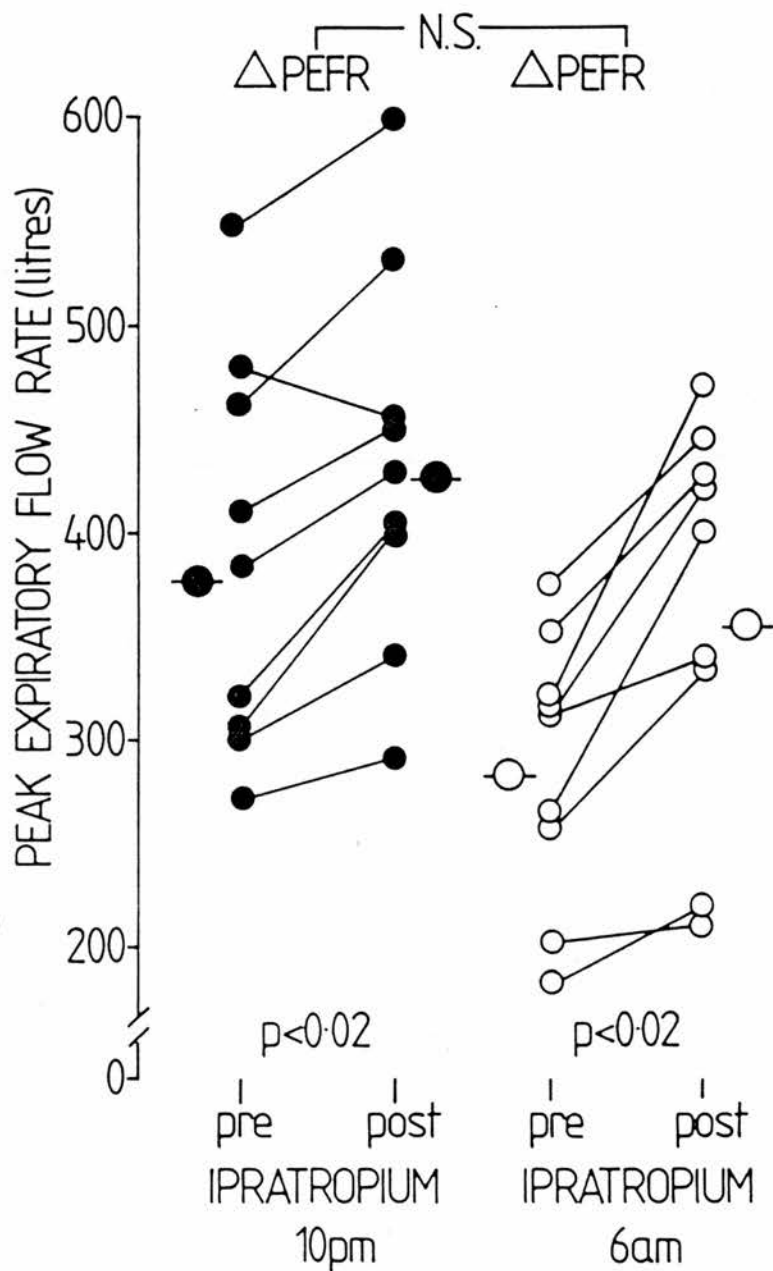
Although ipratropium increased nocturnal peak flow rates significantly, it had no effect on the overnight change in peak flow. Significant bronchoconstriction occurred overnight on both the ipratropium night (PEFR drop from 11.30 pm level to lower of 2 am or 6 am levels  $86 \pm 17$  l/min;  $p < 0.001$ ; fig 29) and the placebo night (PEFR drop  $103 \pm 23$  l/min;  $p < 0.01$ ; fig 29) and these decreases in peak flow were not significantly different on the two nights ( $p > 0.2$ ; fig 29).

#### Effect of ipratropium on peak expiratory flow before and after sleep

There was no significant difference between the bronchodilatation at 6 am on the placebo night and the initial bronchodilatation at 10 pm on the ipratropium night (PEFR rise at 10 pm  $46 \pm 12$  l/min; at 6 am  $83 \pm 17$  l/min;  $p > 0.05$ ; fig 30).



**Fig 29** Maximal overnight fall in peak expiratory flow rate in 10 asthmatic patients on a night when they received ipratropium (closed circles) and a night when they received placebo (open circles).



**Fig 30** Change in peak expiratory flow rate with ipratropium before sleep and after sleep in 9 patients with asthma. The "before sleep" measurements (closed circles) were made at 10 pm on the ipratropium night. The "after sleep" measurements (open circles) were made at 6 am on the placebo night.

#### Effect of ipratropium on PEF at 6 am

Ipratropium at 6 am on the placebo night produced a significant increase in PEF of  $83 \pm 17$  l/min (before ipratropium  $283 \pm 21$  l/min: after ipratropium  $366 \pm 32$  l/min;  $p < 0.01$ ). On the ipratropium night, however, ipratropium did not produce significant additional bronchodilatation at 6 am (before ipratropium  $347 \pm 37$  l/min: after ipratropium  $369 \pm 40$  l/min;  $p > 0.1$ ).

#### Pulse

The pulse rate at the start of the study (10 pm) was not significantly different from the pulse rate at either 11.30 pm, 2 am or 6 am on either the placebo night or the ipratropium night.

#### Effect of terbutaline after maximal bronchodilatation with ipratropium

On both nights, the inhaled terbutaline at 7.30 am produced significant bronchodilatation over and above that brought about by ipratropium. Peak flow rose from  $368 \pm 25$  l/min before terbutaline to  $443 \pm 25$  l/min after terbutaline ( $p < 0.001$ ).

#### Effect of nocturnal ipratropium on the response to metacholine challenge at 6 am

In the additional study involving methacholine challenge, ipratropium again raised the overnight peak flow readings. PEF at 6 am in these four patients averaged  $298 \pm 21$  l/min on the ipratropium night and  $163 \pm 42$  l/min on the placebo night ( $p < 0.05$ ).



**TABLE 10**

**THE EFFECT OF IPRATROPIUM (1 mg), ADMINISTERED AT 10 pm AND 2 am,  
ON THE RESPONSE TO METHACHOLINE CHALLENGE AT 6 am  
IN FOUR PATIENTS WITH ASTHMA**

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Subject No	PC <sub>20</sub> for methacholine at 6 am (ug/ml)	
	Ipratropium night	Placebo night

---

5	8	< 0.05
11	0.05	< 0.03
16	0.5	0.1
20	1.8	< 0.03

---

The subject number is taken from table 7.

In one subject, the FEV<sub>1</sub> at 6 am on the placebo night was only 0.9 l. Since methacholine challenge is contraindicated in patients with a pre-challenge FEV<sub>1</sub> of less than 1 litre (Pepys and Davies, 1977), this patient was given 2 puffs (500 ug) of terbutaline before performing the challenge. This raised the pre-challenge FEV<sub>1</sub> on the placebo night to 2.1 l in this patient.

The effect of ipratropium (1 mg) given at 10 pm and 2 am was to increase the dose of methacholine necessary to produce a 20% fall in FEV<sub>1</sub> at 6 am. On average, the PC<sub>20</sub> for methacholine was approximately 10 times greater on the ipratropium night than on the placebo night (table 10).

### Sleep

In the four subjects whose EEG sleep stages were recorded throughout both nights, time in bed was similar on the ipratropium night ( $400 \pm 3$  min including the interruption at 2 am) and placebo night ( $398 \pm 4$  min; NS). There was a tendency for patients to spend more time awake on the placebo night ( $128 \pm 31$  min) than the ipratropium night ( $89 \pm 13$ ;  $p > 0.05$ ) but this difference did not reach statistical significance with the small number of patients involved. Total sleep time (ipratropium  $312 \pm 11$  min: placebo  $273 \pm 35$  min) and time spent in stage 2 sleep (ipratropium  $93 \pm 16$  min: placebo  $73 \pm 9$  min) tended to be greater on the ipratropium night than the placebo night, although these again were not significant differences. The number of minutes spent in EEG sleep stage 1 (ipratropium  $17 \pm 4$  min:

placebo  $17 \pm 2$  min; NS), slow wave sleep (EEG sleep stages 3 plus 4, ipratropium  $131 \pm 14$  min: placebo  $133 \pm 20$  min; NS) and REM sleep (ipratropium  $64 \pm 6$  min: placebo  $66 \pm 11$  min; NS) were each similar on active drug and placebo.

### DISCUSSION

The main purpose of this study was to determine whether nocturnal bronchoconstriction in asthma is due to increased vagal tone at night. The results suggest that it is not. Ipratropium did increase nocturnal peak flow rates in these patients, but the effect of ipratropium was no greater during the night than before sleep.

To maximise vagal blockade throughout the night in this study, the patients were given 1,000 ug of ipratropium (2-4 times the dose which produced maximal bronchodilatation in these patients) and the drug was administered both before sleep and halfway during the night. This regimen of ipratropium protected against methacholine challenge at 6 am (table 10), with, on average, more than a ten fold increase in the  $PC_{20}$  for methacholine on the ipratropium night compared to the placebo night. Further evidence that there was overnight vagal blockade was provided by the results of the 6 am ipratropium inhalation (fig 28). On the night that the patients received 1 mg of the active drug, they showed no significant additional bronchodilatation at 6 am, whereas ipratropium at the end of the placebo night produced a highly significant rise in peak flow (fig 30). Taken together, these results suggest that there was

substantial blockade of resting vagal tone of the airways in these patients throughout the night that they received ipratropium. Since there was no greater fall in peak flow on the ipratropium night than on the placebo night, changes in airway vagal tone seem unlikely to be important in the pathogenesis of nocturnal bronchoconstriction.

In the cardiovascular system, vagal blockade can be assessed during sleep by measurement of heart rate or of sinus arrhythmia (Soutar et al, 1977; Postma et al, 1985). In this study, heart rate was not significantly different on the ipratropium and placebo nights, but this would not be expected since ipratropium is very poorly absorbed into the systemic circulation, when given by inhalation (Deckers, 1975; Rominger, 1979).

Despite maximal bronchodilatation with ipratropium, the beta-agonist terbutaline produced an additional rise in peak expiratory flow. This rise in peak flow was unlikely to be due to spontaneous bronchodilatation, for it was a large increase over a period of only 30 minutes.

These results - suggesting no increase in airway vagal tone at night in adult patients with asthma - are at variance with those of Gaultier and colleagues (1977) who studied healthy children. They found that ipratropium had greater effects on lung resistance at 8 am than at 11 pm and that ipratropium abolished circadian changes in dynamic compliance. The results of Gaultier and colleagues are difficult to interpret, however, because measurements were made 10

minutes after ipratropium inhalation whereas the peak effect is at 60 - 120 minutes (Gross, 1975; Douglas et al, 1979c; Bruderman et al, 1983).

Other suggestions that increased vagal tone at night might contribute to nocturnal bronchoconstriction have been based on more circumstantial evidence. Reinhardt and colleagues (1980) found that urinary cyclic guanosine monophosphate (c-GMP) levels increase at night in asthmatic children and they suggested that this may reflect increased vagal tone at night. However, the relationship between c-GMP levels and vagal tone is uncertain. Soutar and colleagues (1977) postulated an increase in vagal tone at night to explain their observation that nocturnal peak flow changes paralleled heart rate changes in three of seven asthmatics, and vagal factors were also implicated by Postma and colleagues (1985) who found that eight patients with chronic airflow limitation and nocturnal bronchoconstriction had slower heart rates and longer sinus arrhythmia gaps than healthy control subjects, the differences being maximal at night. Whilst the results of all these studies are consistent with an increase in vagal tone at night, at least in the heart, they are not proof of this, nor do they establish a causal relationship between vagal activity and nocturnal bronchoconstriction.

Although ipratropium did not alter the magnitude of the "nocturnal

dip" (Turner-Warwick, 1977) in these patients, it did cause a substantial improvement in the absolute level of peak flow during the night. This could have useful implications for the treatment of nocturnal asthma. Since quaternary ammonium atropine derivatives such as ipratropium have a longer duration of action (4-6 hours) (Gross, 1975; Ulmer, 1975; Douglas et al, 1979c; Coe and Barnes, 1986) than the  $\beta_2$  agonist inhalers, and since the combination of ipratropium and a  $\beta_2$  agonist usually produces better and more prolonged bronchodilatation than either drug alone (Hebrog, 1975; Lightbody et al, 1978; Douglas et al, 1979d; Ruffin et al, 1982; Lefcoe et al, 1982; Elwood et al, 1982; Bruderman et al, 1983), it seems likely that ipratropium given at night might reduce the need for oral bronchodilators (theophyllines and oral  $\beta_2$  agonists) in some patients. However, further studies will be needed to test this hypothesis, since the duration of action of ipratropium is not quite so long as that of many oral preparations and an additive effect between anticholinergic agents and inhaled  $\beta_2$  agonists has not been demonstrated during the night (Cox et al, 1984). The results of two recent studies (Cox et al, 1984; Coe and Barnes, 1986), both performed concurrently with the present investigation, suggest that anticholinergic agents given as a single dose before sleep may indeed improve nocturnal bronchoconstriction, at least in some asthmatic patients (Coe and Barnes, 1986).

There was a tendency for ipratropium to improve the duration and depth of sleep in these patients. If this is confirmed in larger numbers of patients, it would be another potential advantage of

ipratropium over oral bronchodilators (see Chapter 8). However, it must be stressed that more studies will be need to clarify the effects of inhaled ipratropium on sleep, since patients were deliberately wakened during this study in order to give them an additional nebulisation at 2 am.

In 1870, Thorowgood emphasised the nocturnal occurrence of asthma and recommended stramonium or belladonna "especially given at night in a full dose" as the most effective treatment. The results of this study suggest that changes in vagal tone are unlikely to account for nocturnal changes in airway calibre. However, they confirm that anticholinergic agents can relieve bronchoconstriction at night, and suggest the need for further clinical studies of ipratropium at night in combination with other inhaled therapy.

## SUMMARY - PART IV

The purpose of this part of the thesis was to clarify the effects of sleep on bronchoconstriction in patients with nocturnal asthma.

This involved the following studies:

1. To determine whether sleep is essential for the development of nocturnal bronchoconstriction, 12 patients with nocturnal asthma were studied on two nights - one when they slept and another when they were kept awake. Peak expiratory flow rate fell on both nights, but both absolute and percentage fall in PEFr were greater when the patients slept.
2. In 4 of these patients, venous levels of catecholamines and corticosteroids were measured throughout the two nights. There was no consistent change in 11-hydroxycorticosteroid levels between the awake night and the asleep night. Adrenaline and noradrenaline levels tended to be higher on the asleep night.
3. To determine whether nocturnal bronchoconstriction is associated with a particular stage of sleep, a further study was performed in which PEFr measurements were made after waking patients from known EEG sleep stages. Eight patients with nocturnal asthma were studied, each on three nights. PEFr was lower after awakenings from REM sleep than after time-matched awakenings from NREM sleep, but this difference was small in relation to total overnight



bronchoconstriction and was only significant in the early part of the night.

4. Since REM-related changes in airway tone in dogs may be mediated vagally, the effects of vagal blockade on nocturnal bronchoconstriction were studied. In a double-blind placebo-controlled trial of ipratropium, involving a further 10 patients with nocturnal asthma, nebulised ipratropium increased nocturnal peak flow rates, but this bronchodilating effect was no greater during the night than before sleep.

The following conclusions were drawn:

1. Sleep is not essential for the development of nocturnal asthma but it does appear to aggravate overnight bronchoconstriction.
2. Patients with asthma may bronchoconstrict more in REM sleep than in NREM sleep. However, this REM effect on airway calibre appears to be small in relation to total overnight bronchoconstriction.
3. The bronchoconstricting effect of sleep is unlikely to be mediated by changes in the circulating levels of corticosteroids or catecholamines.
4. Nocturnal bronchoconstriction in asthma is probably not caused by changes in airway vagal tone.

5. Although ipratropium does not abolish overnight bronchoconstriction in asthma, it can raise peak expiratory flow rates during the night as well as during the day. In view of the long duration of action of ipratropium, further studies should be performed to assess the usefulness of this drug in the management of nocturnal asthma.

PART V

CLINICAL IMPLICATIONS AND CONCLUSIONS

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## Chapter 13

### THE CLINICAL IMPLICATIONS OF THESE STUDIES

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The results of this thesis are discussed in detail after each individual study. This chapter contains a brief resume of their main clinical implications.

#### 1. The indications for studies of breathing and oxygenation during sleep

In routine patient care, the major indication for studying breathing and oxygenation during sleep is to confirm a clinical suspicion of the sleep apnoea syndrome. The results of this thesis suggest that expensive sleep studies are not necessary to predict the level of hypoxaemia during REM sleep in patients with either asthma or chronic bronchitis and emphysema, for the lowest oxygen tension during sleep can, within moderately tolerance limits, be predicted from the oxygen tension when awake in these patients (Section III). It must be remembered, however, that obstructive airways disease and sleep apnoea can occasionally coexist, and sleep studies should be performed in patients suspected of having both conditions.

Recent guidelines (Martin et al, 1985) endorsed by the American College of Chest Physicians and the Association of Sleep Disorders Centers, suggest that cardiopulmonary sleep studies may be indicated in patients with chronic obstructive pulmonary disease or asthma if they have sleep-related respiratory symptoms (nocturnal cough or choking, wheezing, sputum production or dyspnoea). However, the asthmatic patients studied in this thesis had normal breathing patterns during sleep, both in terms of the number of apnoeas and hypopnoeas and the duration of inspiration and expiration for each breath. They also had similar falls in oxygen tension during sleep to the normal subjects and bronchitic patients, even though they had nocturnal wheeze, dyspnoea or cough at night, with documented nocturnal bronchoconstriction.

In asthma, therefore, most respiratory symptoms at night do not in themselves appear to be an indication for complex measurements of breathing patterns and oxygenation during sleep, although further studies in larger numbers of patients will be needed to confirm this. For the most part, sleep studies should be restricted to patients who have symptoms suggestive of a sleep apnoea syndrome, (e.g. daytime somnolence, personality change, sexual impotence, morning headache, loud snoring) irrespective of the presence or absence of co-existing lung disease.

It should be stressed, however, that these considerations apply only to the complex studies of breathing and oxygenation described in sections I - III of this thesis. Measurements of circadian changes

in airway calibre ( $FEV_1$  and PEF<sub>R</sub>) are simple, inexpensive, and very useful in the assessment of patients with airflow limitation (Turner-Warwick, 1977).

Furthermore, these comments apply only to routine patient care. Nocturnal asthma remains poorly understood, and its treatment unsatisfactory, and these problems will be resolved only by further research.

## **2. The interpretation of studies of breathing and oxygenation during sleep**

The results reported in section II indicate that there is a wide normal range of apnoea, hypopnoea and oxygen desaturation during sleep, especially in subjects over the age of 50 yr. Indeed, some of our asymptomatic subjects had more than the 30 apnoeas per night required to diagnose a sleep apnoea syndrome (Guilleminault et al, 1978), yet they did not develop symptoms of the syndrome over a follow-up period of six years.

Although the currently accepted definition of a sleep apnoea syndrome is adequate in most clinical settings, these observations suggest that it may not always be applicable, especially over the age of 50 yr. These results suggest, therefore, that the sleep apnoea syndrome should be diagnosed only in patients who have both symptoms suggestive of this syndrome and documented breathing abnormalities during sleep.

These results also emphasise the importance of age-matched controls in studies of breathing and oxygenation during sleep.

In sections II and III of the thesis, hypoxaemia during sleep was shown often to result from hypopnoea rather than apnoea, yet sleep hypopnoea has received little attention in clinical studies. Recent studies suggest that there may be a "sleep hypopnoea syndrome" in which recurrent hypopnoea during sleep - but not apnoea - is associated with clinical features normally found in the sleep apnoea syndrome (Gould et al, 1986). If this observation is confirmed, clinical studies should take into account not only the number of apnoeas during sleep but also the number and duration of hypopnoeas.

### **3. The management of nocturnal asthma**

Patients with bronchial asthma who complain of nocturnal wheeze are often treated with oral theophyllines or oral beta sympathomimetic agents. Although these agents are often necessary to achieve adequate relief of nocturnal symptoms, this approach to treatment is unsatisfactory from both practical and theoretical viewpoints. Practically, these agents are often poorly tolerated and they are not always effective. On theoretical grounds, they are unsatisfactory because they provide symptomatic relief only and do not correct the underlying abnormality. Ideally the treatment of nocturnal asthma should involve a more systematic approach, as outlined below:

#### **3(i) Reduction of bronchial hyperreactivity**

Nocturnal asthma is an exaggeration of the normal reduction in airway

calibre at night. It therefore reflects bronchial hyperreactivity and indicates that the patient's asthma is inadequately controlled. The initial treatment of choice for nocturnal wheeze, therefore, is to increase conventional daytime maintenance treatment with prophylactic agents and, if necessary, inhaled beta<sub>2</sub>-agonists (Connolly, 1981; Horn et al, 1984).

Bronchial hyperreactivity, with parallel improvement in morning peak expiratory flow, can be achieved by rigorous exclusion of inhaled allergens for prolonged periods (Platts-Mills et al, 1982), but this is rarely feasible in practice.

The studies in this thesis do not address the question of bronchial hyperreactivity directly, but it should be the primary consideration in the treatment of all patients with asthma.

### 3(ii) Identification and reversal of the factors which lead to airway narrowing at night

Another approach to the treatment of nocturnal asthma would be to identify the change or changes which lead to airway narrowing at night and to reverse them in patients with asthma. Since nocturnal bronchoconstriction in asthma is an exaggeration of the normal variation in airway calibre at night, it is likely, although not proven, that the immediate cause or causes of nocturnal bronchoconstriction are physiological.

There have been many attempts to identify the nature of these changes



(Douglas, 1983 and 1985; Barnes, 1984) and the studies in section IV - in which I attempted to define the relationship between sleep and bronchoconstriction - fall into this category.

The study in chapter 10 demonstrated that partial relief of nocturnal bronchoconstriction could be achieved by keeping patients awake all night, but clearly this has no direct practical application. Furthermore, it did not distinguish the effects of sleep itself from those of other circadian changes which might have been affected by disruption of the sleep-wake cycle. A further study established a relationship between bronchoconstriction and REM sleep, but the effect of REM sleep was small compared to the overall nocturnal change in peak flow and was only significant in the early part of the night. Although it might have been possible to reduce the amount of REM sleep by giving patients the tricyclic antidepressant propryptiline, an approach that has been shown to improve symptoms (Brownell et al, 1982; Conway et al, 1982), nocturnal oxygenation (Brownell et al, 1982; Smith et al, 1982) and the number of apnoeas (Clark et al, 1979; Conway et al, 1972; Smith et al, 1982) in patients with the obstructive sleep apnoea syndrome, I was reluctant to use this approach since the REM effect on airway calibre was small and this agent sometimes has adverse anticholinergic effects, even when used at night (Conway et al, 1982). Instead, I postulated that the REM effect on airway calibre (and also some of the overnight bronchoconstriction that was not associated with REM sleep) might be due to increased vagal tone. However, I found no evidence for this. Although the inhaled anticholinergic agent ipratropium improved

airway calibre overall, the overnight effect of ipratropium was no greater than its effect at 10 pm, before sleep.

Other studies attempting to define the mechanism of nocturnal bronchoconstriction have also been disappointing in their practical application. Reinberg and colleagues (1969) noted that circulating catecholamines showed circadian changes with a nocturnal nadir. These observations were extended by Soutar and colleagues (1977) who found that urinary catecholamine excretion fell to a minimum coincidental with the lowest peak flow rates in seven asthmatics, and by Barnes and co-workers (1980) who demonstrated a temporal relationship between the circulating catecholamine level and nocturnal bronchoconstriction. Barnes and colleagues also showed that nocturnal peak flow rates could be improved by infusion of adrenaline but the adrenaline was infused for only 10 minutes on three separate occasions and the authors did not report the resulting plasma adrenaline levels. It is uncertain, therefore, whether the effect of the infused adrenaline was due only to reversal of the nocturnal fall in circulating adrenaline or whether the adrenaline levels were supraphysiological. Other studies have shown that, although supraphysiological doses of betasympathomimetic agents may help nocturnal asthma, they do not abolish morning dipping (Turner-Warwick, 1977; Milledge and Morris, 1979; Fairfax et al, 1980; Fairfax, 1984).

Reinberg and colleagues (1963) showed that nocturnal breathlessness in asthmatic patients was most marked when the urinary excretion of

17-hydroxycorticosteroids was at its lowest. Soutar and colleagues (1975) confirmed that peak flow rates paralleled changes in circulating corticosteroids, but proved that this was not a causal relationship by showing that overnight fall in peak flow was unchanged if 11-hydroxycorticosteroid levels were kept constant overnight by infusion of hydrocortisone. Thus circadian changes in circulating cortisol seem unlikely to be the immediate cause of nocturnal bronchoconstriction. There is evidence that regular treatment with corticosteroids will reduce morning dipping (Horn et al, 1984) but this is presumably an effect on overall airway stability (see above) rather than a pure nocturnal effect.

Nocturnal cooling of the airways (Chen and Chai, 1982), gastrooesophageal reflux at night (Martin et al, 1982; Davis et al, 1983; Hughes et al, 1983; Inouye et al, 1984) and impairment of mucociliary clearance during sleep (Bateman et al, 1978) have all been postulated as possible causes of nocturnal bronchoconstriction but in none of these studies has the evidence been conclusive (Douglas, 1985) and at present there is no indication that correction of these factors has any practical clinical application.

To date, therefore, attempts to identify and correct the immediate cause of nocturnal bronchoconstriction have been disappointing, with little direct benefit to the patient. It is possible that nocturnal bronchoconstriction could result from a combination of factors, each of differing importance in different individuals. This emphasises the importance of dealing with the underlying abnormality in

nocturnal asthma, i.e. the increased bronchial hyperreactivity, discussed above.

### 3(iii) Symptomatic treatment

The studies in section III of the thesis showed that asthmatic patients not only bronchoconstrict at night, but also that they sleep less well and become more hypoxaemic at night than healthy control subjects. The ideal treatment regimen for nocturnal asthma should restore all of these changes to normality. Unfortunately, however, neither oral theophyllines nor oral beta agonists - which can reduce the overnight fall in peak flow (Milledge and Morris, 1979; Fairfax et al, 1980; Barnes et al, 1982; Davies et al, 1984; Fairfax, 1984) - improve the quality of sleep in asthma (Rhind et al, 1985; Stuart et al, 1984). Indeed, theophyllines actually disrupt sleep in both asthmatic patients (Rhind et al, 1985) and patients with chronic obstructive pulmonary disease (Fleetham et al 1983). A recent report (Stewart et al, 1984) indicates that oral terbutaline does not affect the duration and quality of sleep in asthma. If this is confirmed, at equal levels of bronchodilatation, oral beta agonists may have an advantage over oral theophyllines for the treatment of nocturnal asthma, but this is uncertain at present.

In this thesis I studied the effects of ketotifen in patients with nocturnal asthma. A single 1 mg dose of ketotifen improved sleep without impairing oxygenation but it did not alter the overnight fall in  $FEV_1$ . Since there is doubt about the effectiveness of this agent as a bronchodilator in clinical practice, even when given for periods

of 4 - 8 weeks (Dyson and Mackay, 1980; Petheram et al, 1981; Monie et al, 1982), ketotifen cannot be recommended for the treatment of nocturnal asthma on current evidence.

In general, inhaled therapy for asthma is preferable to oral therapy, since similar levels of bronchodilation occur with much lower doses and thus adverse systemic effects are minimised (Larsson and Svedmyr, 1977; Rossing et al, 1980; Williams et al, 1981; McFadden, 1986). The main reason for using oral agents to treat nocturnal asthma is their longer duration of action than inhaled beta agonists. The observation (Chapter 12; Cox et al, 1984; Coe and Barnes, 1986) that ipratropium increases nocturnal peak flow rates is of interest in this context, for this agent also has a longer duration of action than inhaled beta agonists (Gross, 1975; Ulmer, 1975; Douglas et al, 1979c). However, the role of inhaled anticholinergic bronchodilators in nocturnal asthma has still to be defined.

## CONCLUSIONS

These investigations have helped to clarify some of the interrelations of asthma and sleep. As noted above, they have also helped to define the role of sleep studies in the management of patients with respiratory disease and they have established normal reference ranges for irregular breathing and oxygenation during sleep.

Sleep is not essential for the development of nocturnal asthma, but it does appear to aggravate bronchoconstriction at night. Patients with asthma may bronchoconstrict more in REM sleep than in non-REM (NREM) sleep, but the bronchoconstricting effect of REM appears to be small in relation to total overnight change in airway calibre. Other mechanisms by which sleep aggravates bronchoconstriction are poorly understood. Nocturnal bronchoconstriction in asthmatic patients does not appear to be due to an increase in airway vagal tone at night.

REM sleep is also associated with hypoventilation, both in asthmatic patients and normal subjects. The consequent falls in arterial oxygen saturation are small in most stable asthmatics, but nocturnal hypoxaemia in REM sleep is probably more pronounced in patients who are hypoxaemic when awake, including those with severe asthma or patients recovering from acute attacks. Such episodes of nocturnal hypoxaemia could contribute to the rare but well-recognised nocturnal deaths from asthma.

These studies have also confirmed that asthma disrupts sleep. Lack of sleep is a common finding in asthma and may lead to impaired performance at work or school in some patients. The ideal treatment regimen in asthma should therefore improve sleep as well as airway calibre. This will best be achieved by the liberal use of prophylactic agents - to reduce bronchial hyperreactivity - and by the development of bronchodilators which act throughout the night without disrupting sleep.

## APPENDIX

Tables 11 - 19 and figures 31 and 32

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TABLE 11

**SLEEP QUALITY IN 19 HEALTHY MEN DURING STUDIES OF NOCTURNAL  
BREATHING PATTERNS AND OXYGENATION**

Subject No	Age (yr)	TIB (min)	TST (min)	SEI (%)	SOL (min)	1	% of TST in	sleep stage	2	3	4	REM
1	23	430	419	97	8	5	38	29	16			11
2	25	430	410	95	4	4	40	7	30			19
3	27	405	367	85	15	10	67	6	8			10
4	27	460	408	89	12	9	54	8	7			22
5	27	468	410	88	17	3	55	5	9			28
6	28	450	423	94	7	5	48	7	17			23
7	28	405	376	93	15	9	58	3	4			26
8	37	374	354	95	6	15	43	8	19			16
9	40	400	373	93	3	10	39	6	16			29
10	42	452	366	81	28	17	46	9	6			23
11	45	421	405	96	12	7	64	5	6			18
12	45	410	396	97	12	14	47	5	7			21
13	51	425	347	82	19	4	66	5	2			23
14	52	473	413	87	8	8	51	7	16			23
15	55	395	294	74	22	11	61	6	10			12
16	57	363	287	79	29	7	59	13	1			19
17	58	425	394	93	10	10	47	8	12			23
18	60	428	223	52	6	6	66	5	6			17
19	68	435	309	71	7	24	58	12	4			2

TIB, time in bed; TST, total sleep time; SEI, sleep efficiency index; SOL, sleep onset latency. See table 3 for summary of results, for comparisons between sexes, and for comparisons between older and younger subjects.

TABLE 12

**SLEEP QUALITY IN 21 HEALTHY WOMEN DURING STUDIES OF  
NOCTURNAL BREATHING PATTERNS AND OXYGENATION**

Subject No	Age (yr)	TIB (min)	TST (min)	SEI (%)	SOL (min)	% of TST in EEG sleep stage				
						1	2	3	4	REM
1	22*	-	-	-	-	-	-	-	-	-
2	23	405	376	93	12	3	37	30	23	7
3	24	420	391	93	6	1	42	17	26	14
4	25	445	404	91	9	4	51	10	21	14
5	26	455	404	89	14	6	51	13	9	21
6	26	420	397	95	5	6	47	3	18	26
7	27	385	346	90	41	6	58	10	10	16
8	32	472	444	94	17	4	60	3	13	19
9	38	448	399	89	17	9	67	3	6	15
10	42	458	409	89	6	6	50	14	9	21
11	46	439	382	87	9	15	53	17	10	5
12	49	445	425	96	2	5	46	7	24	18
13	50	370	333	90	4	6	54	10	11	19
14	50	457	424	93	7	6	51	6	10	27
15	53	400	386	96	11	5	54	6	9	26
16	55	403	298	74	10	10	58	9	7	16
17	55	450	309	69	54	10	60	18	0	12
18	60	438	413	94	5	9	69	5	4	15
19	63	398	351	88	6	8	59	6	8	19
20	64	386	369	96	2	5	68	6	0	20
21	64	436	409	94	16	3	50	11	5	31

\*The EEG, EOG and EMG traces were of poor quality in this subject. TIB, time in bed; TST, total sleep time; SEI, sleep efficiency index; SOL, sleep onset latency. See table 3 for summary of results, for comparisons between sexes and for comparisons between older and younger subjects.

TABLE 13

## BREATHING PATTERNS DURING SLEEP IN 19 HEALTHY NON-OBESE MEN

Subject No	Age (yr)	Weight (% average)	Apnoeas	Hypopnoeas	Irregular breathing (min)				
					Total	In sleep stages:			
						1	2	3+4	REM
1	23	100	0	0	0	0	0	0	0
2	25	99	0	4	5	0	0	0	5
3	27	91	0	2	1	0	0	0	1
4	27	104	0	0	0	0	0	0	0
5	27	100	0	2	1	0	0	0	1
6	28	102	0	0	0	0	0	0	0
7	28	104	0	0	0	0	0	0	0
8	37	100	1	0	1	0	1	0	0
9	40	89	6	0	9	0	0	0	9
10	42	87	3	1	5	0	0	0	5
11	45	100	0	0	0	0	0	0	0
12	45	102	2	0	2	0	0	0	2
13	51	94	45	40	123	17	26	4	76
14	52	95	2	8	18	1	4	0	13
15	55	99	1	2	4	0	0	0	4
16	57	101	0	4	6	0	0	0	6
17	58	105	10	11	28	0	7	0	21
18	60	101	2	9	14	0	2	0	12
19	68	88	13	54	68	12	50	0	6

Average body weights taken from Documenta Geigy, 1970.

See table 3 and figure 6 for summary of results, for comparisons between sexes and for comparisons between older and younger subjects.

TABLE 14

## BREATHING PATTERNS DURING SLEEP IN 21 HEALTHY NON-OBESE WOMEN

Subject No	Age (yr)	Weight (% average)	Apnoeas	Hypopnoeas	Irregular breathing (min) Total	In sleep stages:			
						1	2	3+4	REM
1	22	104	0	2	2	0	0	0	2
2	23	102	0	7	12	0	2	0	10
3	24	94	0	1	1	0	0	0	1
4	25	105	0	0	0	0	0	0	0
5	26	100	1	0	1	0	1	0	0
6	26	105	0	0	0	0	0	0	0
7	27	101	0	0	0	0	0	0	0
8	32	105	0	0	0	0	0	0	0
9	38	85	0	0	0	0	0	0	0
10	42	97	0	3	6	0	0	0	6
11	46	105	1	2	4	0	0	0	4
12	49	98	1	2	4	0	0	0	4
13	50	100	0	0	0	0	0	0	0
14	50	87	1	0	1	0	0	0	1
15	53	93	0	2	3	0	0	0	3
16	55	91	0	9	17	0	0	0	17
17	55	102	9	11	36	2	16	0	18
18	60	95	75	9	120	12	59	0	49
19	63	100	1	35	47	2	10	0	35
20	64	112	0	4	6	0	0	0	6
21	64	88	4	13	21	0	0	0	21

Average body weights taken from Documenta Geigy, 1978.

See table 3 and figure 6 for summary of results, for comparison between sexes, and for comparison between older and younger subjects.

TABLE 15

## ARTERIAL OXYGEN SATURATION DURING SLEEP IN 19 HEALTHY NON-OBESE MEN

Subject No	Age (yr)	SaO <sub>2</sub>		No of H.E.'s	H.E.'s in sleep stage:			H.E.'s with		
		Awake (%)	Lowest (%)		1	2	REM	Reg	Hy	Ap
1	23	98	93	0						
2	25	96	94	0						
3	27	98	96	0						
4	27	98	96	0						
5	27	99	93	0						
6	28	95	90	0						
7	28	96	94	0						
8	37	99	93	0						
9	40	98	93	1		1				1
10	42	98	93	0						
11	45	98	92	0						
12	45	98	95	0						
13	51	98	93	3			3		2	1
14	52	96	92	0						
15	55	94	89	0						
16	57	98	94	1			1		1	
17	58	97	93	0						
18	60	95	88	2	1		1		1	1
19	68	95	71	6		5	1		3	3

SaO<sub>2</sub>, arterial oxygen saturation (measured by ear oximetry) awake or at lowest level during sleep; H.E., hypoxaemic episode; Reg, regular breathing; Hy, hypopnoea; Ap, apnoea. See table 3 and figure 7 for summary of results, for comparison between sexes, and for comparison between older and younger subjects.

TABLE 16

## ARTERIAL OXYGEN SATURATION DURING SLEEP IN 21 HEALTHY NON-OBESE WOMEN

Subject No	Age (yr)	SaO <sub>2</sub>		No of H.E.'s	H.E.'s in sleep stage:			H.E.'s with		
		Awake (%)	Lowest (%)		1	2	REM	Reg	Hy	Ap
1	22	95	93	0						
2	23	97	90	1			1		1	
3	24	97	93	0						
4	25	98	94	0						
5	26	97	93	0						
6	26	97	95	0						
7	27	97	95	0						
8	32	98	94	0						
9	38	99	96	0						
10	42	97	93	0						
11	46	97	90	1			1	1		
12	49	95	93	0						
13	50	97	92	0						
14	50	96	93	0						
15	53	96	94	0						
16	55	97	90	1			1		1	
17	55	95	87	1			1			1
18	60	96	72	4		2	2		3	1
19	63	97	78	5		2	3	1	4	
20	64	95	94	0						
21	64	96	92	2			2		2	

SaO<sub>2</sub>, arterial oxygen saturation (measured by ear oximetry) awake or at lowest level during sleep; H.E., hypoxaemic episode; Reg, regular breathing; Hy, hypopnoea; Ap, apnoea. See table 3 and figure 7 for summary of results, for comparison between sexes, and for comparison between older and younger subjects.

TABLE 17

**SLEEP QUALITY IN 20 INDIVIDUAL PATIENTS WITH CHRONIC ASTHMA**  
**DURING STUDIES OF NOCTURNAL BREATHING PATTERNS AND OXYGENATION**

Patient No	Age (yr)	FEV <sub>1</sub> (%)	TIB (min)	TST (min)	SEI (%)	SOL (min)	% Total sleep time in	1	2	3	4	EEG stage: REM
1	18	29	397	310	78	19	4	70	8	0	8	
2	18	63	420	346	77	50	4	53	6	22	15	
3	21	27	437	389	89	19	11	56	6	9	18	
4	21	12	324	268	83	18	4	59	5	26	7	
5	22	42	431	370	86	12	9	48	7	18	18	
6	23	50	436	332	63	37	15	60	4	8	13	
7	27	38	416	360	86	24	17	45	5	26	7	
8	30	38	356	257	72	16	22	51	5	2	20	
9	34	14	420	342	81	32	7	62	4	18	9	
10	34	52	388	218	69	23	23	41	6	14	16	
11*	37	–	550	266	48	145	13	40	9	14	24	
12	39	27	570	284	50	189	14	66	8	4	8	
13	40	11	382	270	71	8	11	43	6	12	28	
14	50	33	403	165	41	23	18	50	5	3	24	
15*	50	–	417	293	51	70	18	53	8	8	13	
16	51	23	406	320	80	4	1	51	6	0	31	
17	53	35	433	245	57	51	13	46	12	20	9	
18	56	19	403	354	88	6	13	71	7	0	11	
19	56	39	410	344	84	11	23	52	5	3	17	
20	59	44	360	206	57	8	16	46	8	19	11	

Patients 11 and 15 used a bronchodilator inhaler before the FEV<sub>1</sub> was measured.

$$\text{FEV}_1\% = \frac{\text{FEV}_1 \text{ before sleep} - \text{lowest FEV}_1}{\text{FEV}_1 \text{ before sleep}} \times 100\%;$$

see table 19 for absolute values of FEV<sub>1</sub>.

TIB, time in bed; TST, total sleep time; SEI, sleep efficiency index; SOL, sleep onset latency.

TABLE 18

BREATHING PATTERNS DURING SLEEP IN 20 PATIENTS WITH ASTHMA

Subject No	Age (yr)	FEV <sub>1</sub> (%)	Apnoeas	Hypopnoeas	Irregular Total	breathing (min) In sleep stages			
						1	2	3+4	REM
1	18	29	0	0	0	0	0	0	0
2	18	63	0	3	6	0	0	0	6
3	21	27	0	0	0	0	0	0	0
4	21	12	0	5	8	0	0	0	8
5	22	42	0	0	0	0	0	0	0
6	23	50	0	3	4	1	0	0	3
7	27	38	0	2	4	4	0	0	0
8	30	38	0	0	0	0	0	0	0
9	34	14	-	-	-	-	-	-	-
10	34	52	0	0	0	0	0	0	0
11*	37	-	8	17	33	9	0	0	24
12	39	27	0	6	10	0	5	0	5
13	40	11	4	30	57	0	0	0	52
14	50	33	2	44	74	21	27	0	26
15*	50	-	0	7	13	9	0	0	4
16	51	23	41	8	44	3	15	0	36
17	53	35	13	2	18	14	0	0	4
18	56	19	38	5	52	4	25	1	22
19	56	39	36	4	42	28	9	0	5
20	59	44	9	10	27	18	6	3	0

\* Patients 11 and 15 used a bronchodilator inhaler before the FEV<sub>1</sub> was measured.

$$FEV_1\% = \frac{FEV_1 \text{ before sleep} - \text{lowest } FEV_1}{FEV_1 \text{ before sleep}} \times 100;$$

see table 19 for absolute values of FEV<sub>1</sub>.



TABLE 19

**ARTERIAL OXYGEN SATURATION DURING SLEEP IN 20 PATIENTS  
WITH CHRONIC ASTHMA**

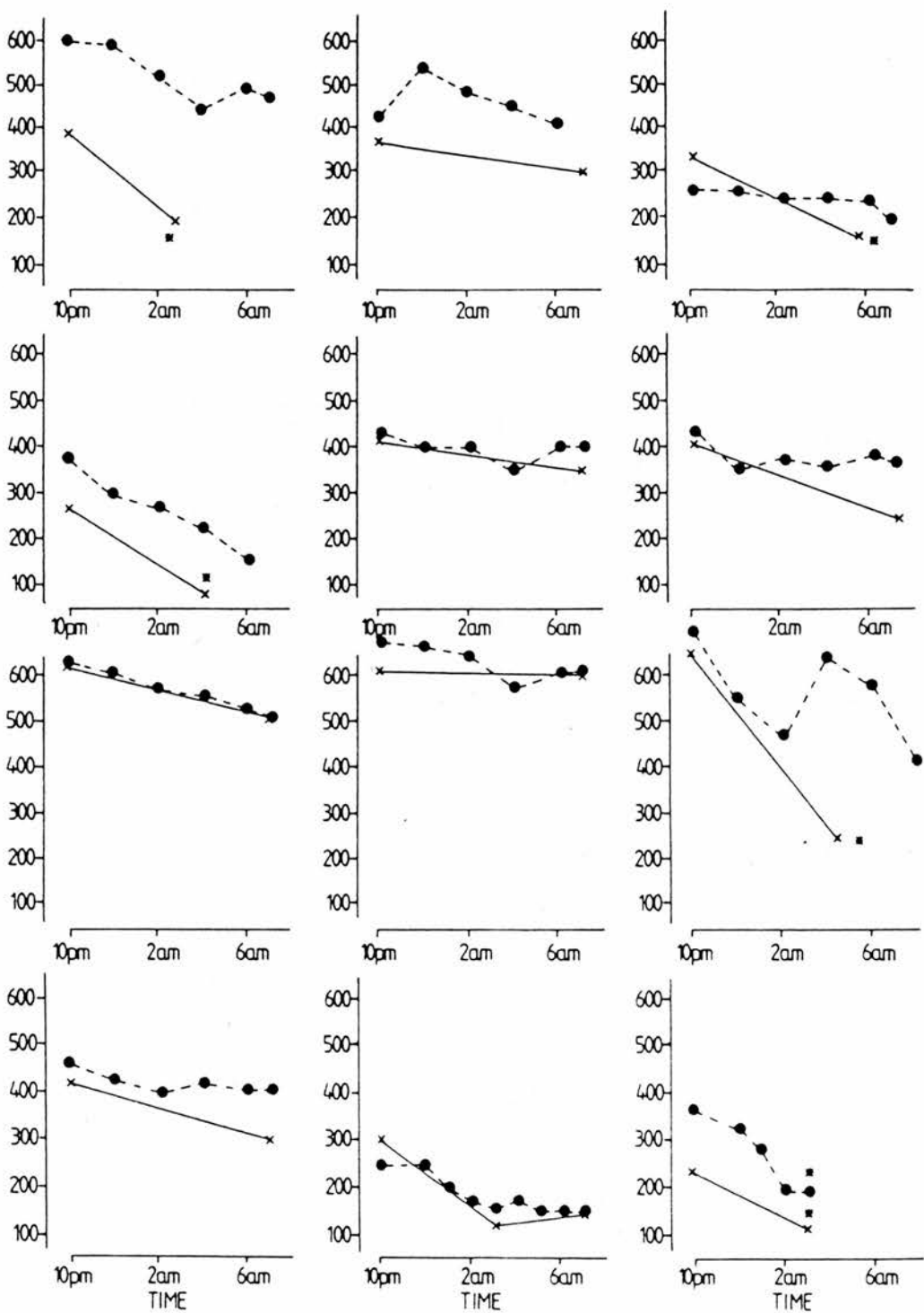
Subject No	Age (yr)	FEV <sub>1</sub> (l)		SaO <sub>2</sub> (%)		No of H.E's	H.E's in sleep stages			H.E's with		
		Pre- sleep	Low- est	Awake	Lowest		1	2	REM	Reg	Hy	Ap
1	18	4.2	3.0	98	93	0						
2**	18	3.8	1.4	95	85	2			2		2	
3	21	3.3	2.4	98	92	0						
4	21	4.2	3.7	93	83	2			2	1	1	
5	22	1.9	1.1	95	89	0						
6	23	3.2	1.6	94	88	1			1	1		
7	27	1.3	0.8	98	94	0						
8**	30	1.3	0.8	94	83	1			1	1		
9***	34	3.6	3.1	97	87	1			1	-	-	-
10**	34	3.3	1.6	98	89	3			3	3		
11*	37	0.8	-	93	86	4	1		3		4	
12	39	1.5	1.1	92	85	1			1		1	
13	40	1.8	1.6	95	87	4			4	1	3	
14**	50	1.2	0.8	96	83	5		3	2	2	3	
15	50	1.4	-	97	86	2			2		2	
16***	51	1.3	1.0	95	78	6		2	4		1	4
17	53	2.3	0.8	91	83	1		1				1
18	56	1.6	1.3	97	77	7	1	3	3	1	2	4
19	56	2.3	1.4	95	84	4		4			1	3
20	59	0.9	0.5	96	88	1			1	1		

SaO<sub>2</sub>, arterial oxygen saturation (ear oximeter) awake or at lowest level during sleep; H.E., hypoxaemic episode; Reg, regular breathing; Hy, hypopnoea; Ap, apnoea.

\* Patients 11 and 15 used a bronchodilator inhaler before the lowest FEV<sub>1</sub> was measured.

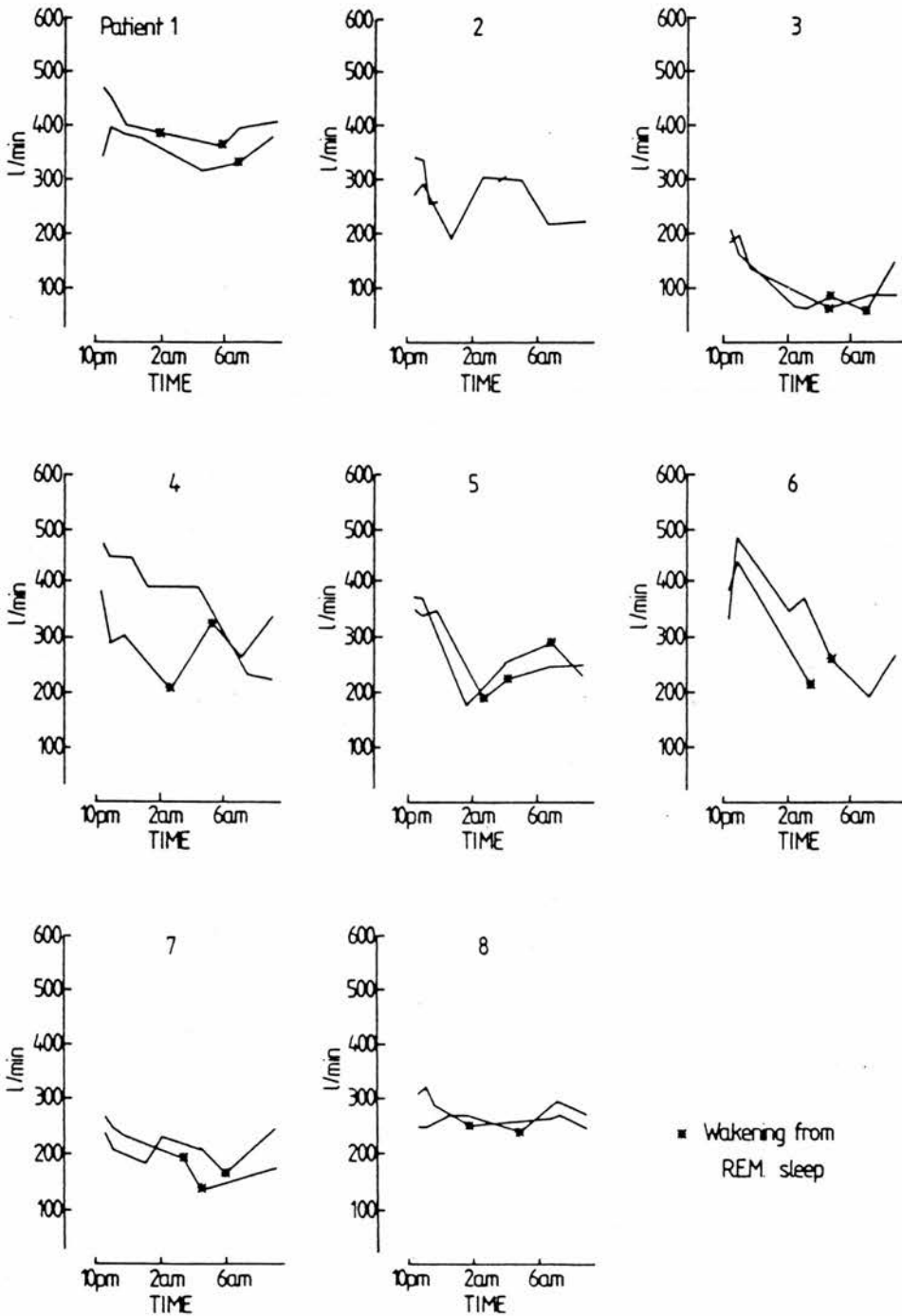
\*\* Patients 2, 8, 10 and 14 woke early and used a bronchodilator inhaler.

\*\*\* The magnetometer trace was unsatisfactory in patient 9 and also during one hypoxaemic episode in patient 16.

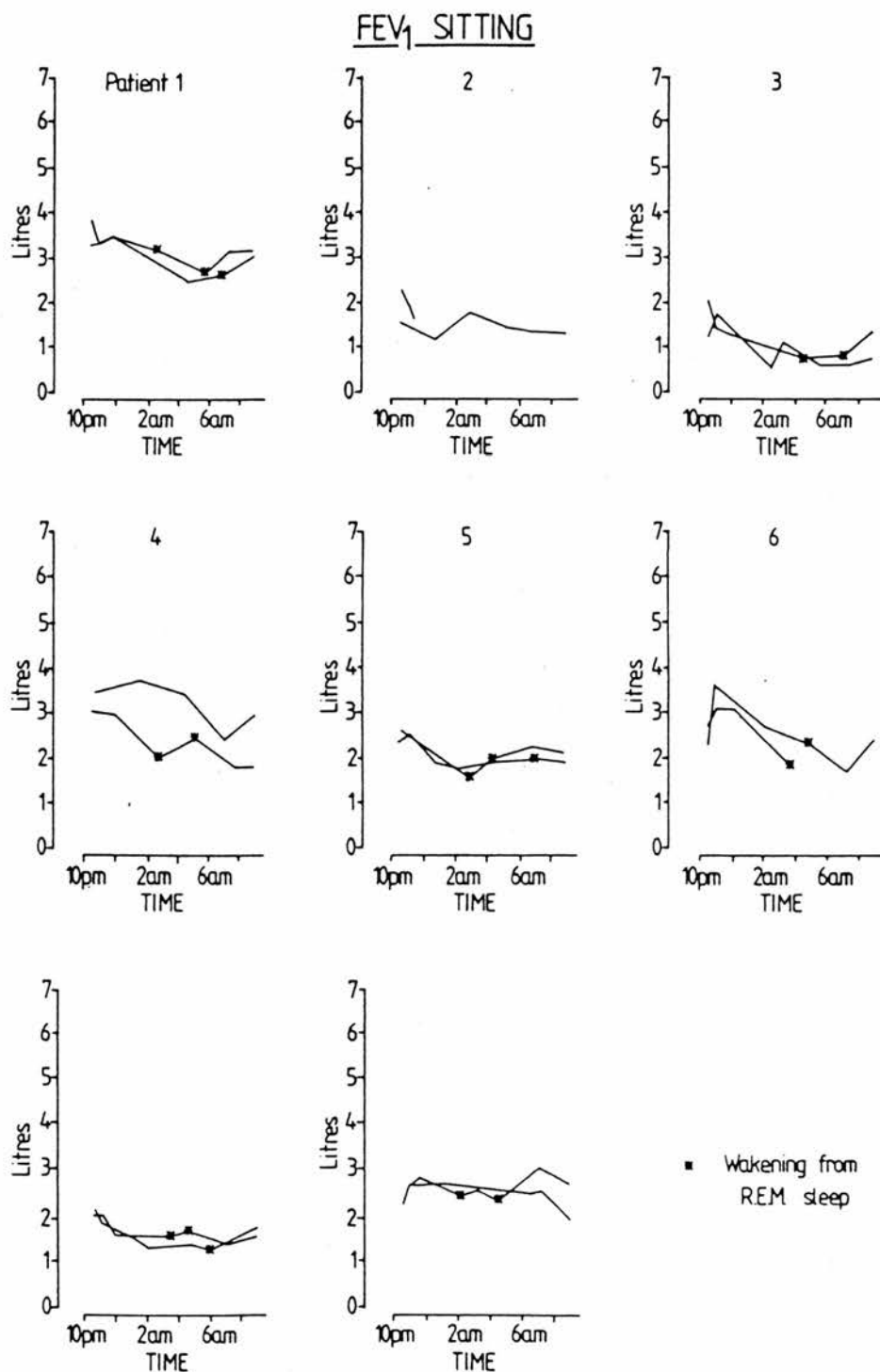


**Fig 31** Peak expiratory flow rates in 12 asthmatic patients on a night when they slept (continuous line) and throughout a night when they were kept awake (broken line).

# PEFR LYING

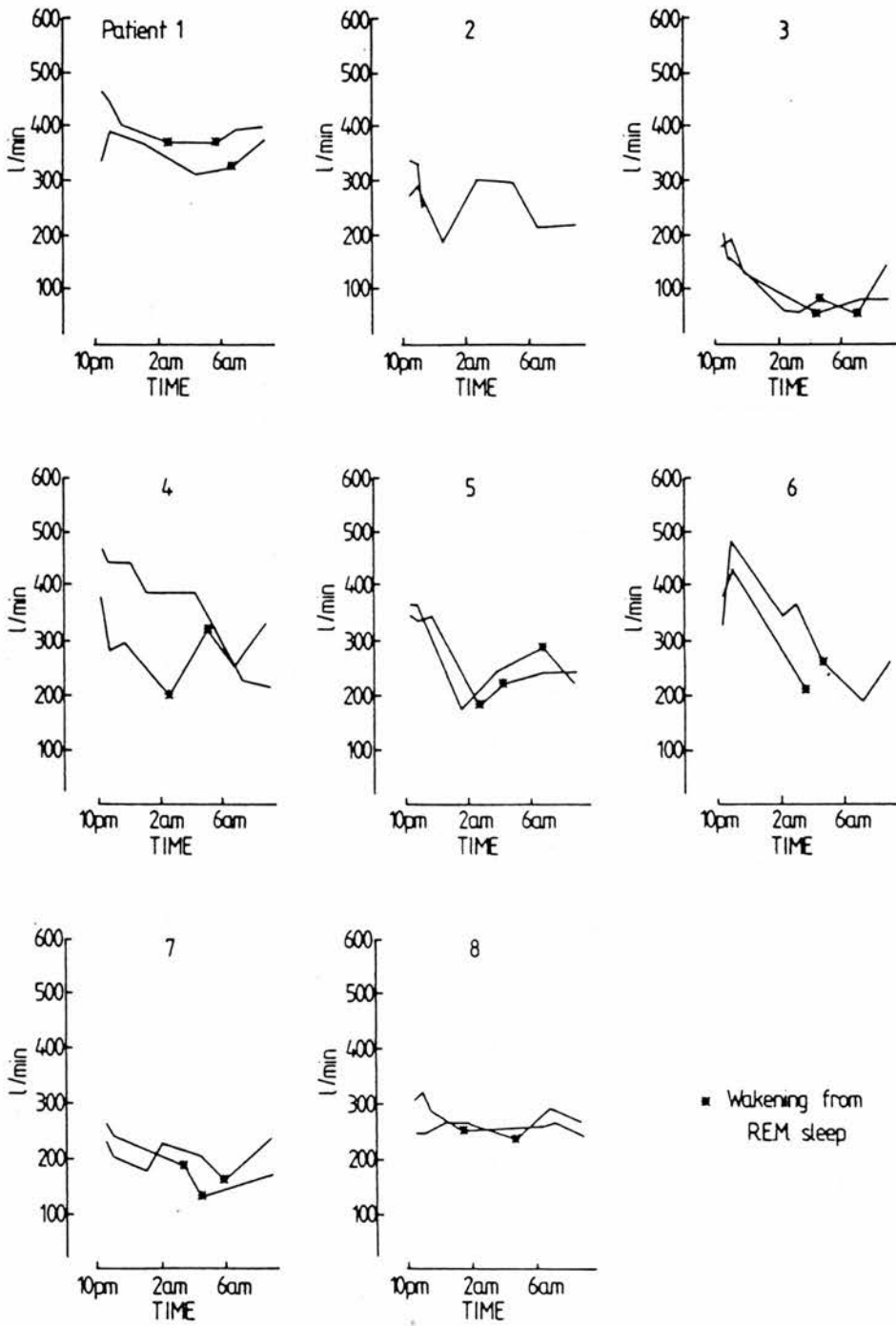


**Fig 32a** PEFR lying in 8 asthmatic patients after deliberate wakenings from REM and NREM sleep. The two lines for each patient represent two separate nights of study and the wakenings from REM sleep are marked with an asterisk. For details, see chapter 11.



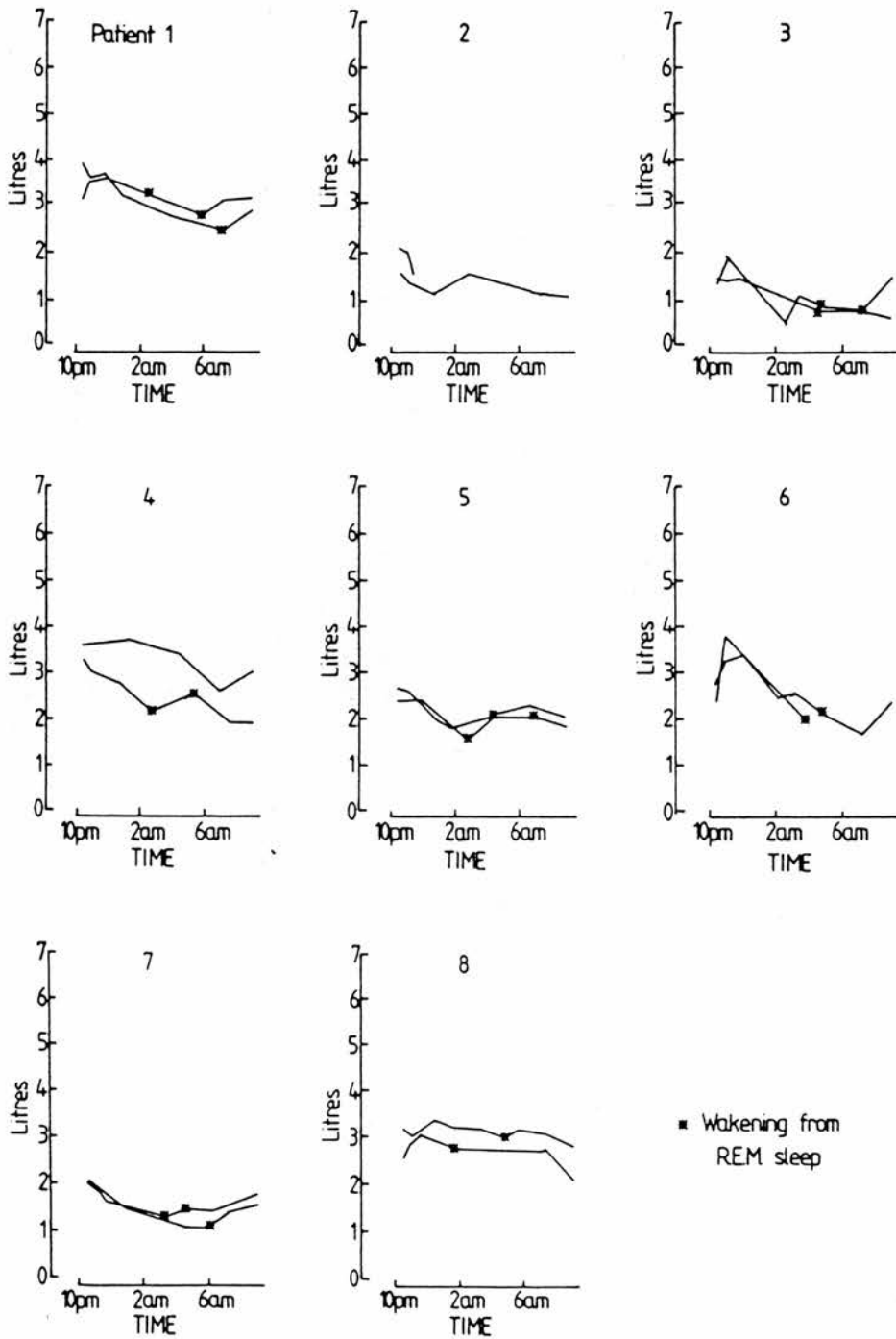
**Fig 32b** FEV<sub>1</sub> sitting in 8 asthmatic patients after deliberate wakenings from REM and NREM sleep on two nights. For details, see chapter 11.

# PEFR STANDING



**Fig 32c** PEFR standing in 8 asthmatic patients after deliberate wakenings from REM and NREM sleep on two nights. For details, see chapter 11.

# FEV<sub>1</sub> STANDING



**Fig 32d** FEV<sub>1</sub> standing in 8 asthmatic patients after deliberate wakenings from REM and NREM sleep on two nights. For details, see chapter 11.

### FORMAL DECLARATION

I declare that I have composed this thesis and that the work is my own.

The studies described in the thesis were performed by a research team of which I was a member. My own contribution was as follows:

1. I performed the great majority of studies in each chapter of the thesis (with the exception of chapter 11, as explained in the text).
2. I analysed and interpreted all the data in the thesis, with the exception of the EEG sleep staging.
3. I took a major part in the initiation and design of the studies. The studies in parts II and II of the thesis were initiated by Professor D C Flenley, and designed by Professor Flenley, Dr N J Douglas and myself. The studies in part IV were initiated and designed jointly by Dr Douglas and myself.

*J.R. Batterall.*

*16<sup>th</sup> December, 1986*

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I am grateful to all the physicians, nurses, technicians, physicists, statisticians, volunteers and patients who helped in the research reported in this thesis. The names of the major collaborators are included in the list of publications. I particularly thank: Professor D C Flenley for stimulating my interest in this field of research, Dr N J Douglas for supervising the investigations, Dr C M Shapiro for staging the electroencephalograms, Dr P K Wraith for writing the computer programmes and Mrs Carol Hoy for nursing and technical assistance.

I also thank Mrs M Miller and Mrs A Parker for drawing the figures and Mrs J Johnstone for typing the thesis.



## PUBLICATIONS

The following publications include work described in this thesis.

1. Catterall J R, Douglas N J, Calverley P M A, Brash H M, Brezinova V, Shapiro C M, Flenley D C (1982). Irregular breathing and hypoxaemia during sleep in chronic stable asthma. *Lancet*; 1: 301-304.
2. Catterall J R, Douglas N J, Calverley P M A, Shapiro C M, Brash H M, Flenley D C (1983). Transient hypoxaemia during sleep in COLD is not a sleep apnea syndrome. *Am Rev Resp Dis*; 129: 24-29.
3. Calverley P M A, Catterall J R, Shapiro C M, Douglas N J (1983). Cor pulmonale in asthma. *Br J Dis Chest*; 77: 303-307.
4. Catterall J R, Calverley P M A, Power J T, Shapiro C M, Douglas N J, Flenley D C (1983). Ketotifen and nocturnal asthma. *Thorax*; 38: 845-848.
5. Catterall J R, Calverley P M A, Shapiro C M, Flenley D C, Douglas N J (1985). Breathing and oxygenation during sleep are similar in normal men and normal women. *Am Rev Resp Dis*; 132: 86-88.

6. Catterall J R, Calverley P M A, MacNee W, Warren P M, Shapiro C M, Douglas N J, Flenley D C (1985). The mechanism of transient nocturnal hypoxaemia in hypoxic chronic bronchitis and emphysema. J Appl Physiol; 59: 1698-1703.
7. Catterall J R, Rhind G B, Stewart I C (1986). Effect of sleep deprivation on overnight bronchoconstriction in nocturnal asthma. Thorax; 41: 676-680.
8. Shapiro C M, Catterall J R, Montgomery I, Raab G M, Douglas N J (1986). Do asthmatics suffer bronchoconstriction in rapid eye movement sleep? Br Med J; 292: 1161-1164.
9. Catterall J R, Morgan A D, Douglas N J, Shapiro C M, Flenley D C (1983). Nocturnal desaturation, breathing patterns and bronchoconstriction in adult asthmatics. Am Rev Resp Dis; 127 (supplement): 106 (abstract).
10. Catterall J R, Rhind G B, Douglas N J (1985). Nocturnal asthma is not caused by increased airway vagal tone. Am Rev Resp Dis; 131 (supplement): 55 (abstract).

The publications in print are included at the end of the thesis, with the permission of the co-authors and publishers.

## REFERENCES

- Agnew H W, Webb W B, Williams R L (1966). The first night effect; an EEG study of sleep. *Psychophysiology*; 2: 263-266.
- Allen C J, Campbell A H (1980). Comparison of inhaled atropine sulphate and inhaled atropine methonitrate. *Thorax*; 35: 932-935.
- Alvin J, McHorse T, Hoyumpa A, Bush M T, Schenker S (1975). The effect of liver disease in man on the disposition of phenobarbital. *J Pharmacol Exp Ther*; 192: 224-235.
- Ancoli-Israel S, Kripke D F, Mason W, Messin S (1981). Sleep apnea and nocturnal myoclonus in a senior population. *Sleep*; 4: 349-358.
- Ancoli-Israel S, Kripke D F, Mason W, Kaplan O J (1985). Sleep apnea and periodic movements in an aging sample. *J Gerontol*; 40: 419-429.
- Ariagno R L, Guilleminault C (1985). Apnea during sleep in the pediatric patient. *Clinics in Chest Medicine*; 6: 679-690.
- Aserinsky E, Kleitman N (1953). Regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science*; 118: 273-274.
- Aserinsky E (1965). Periodic respiratory pattern occurring in conjunction with eye movements during sleep. *Science*; 150: 763-766.
- Askanazi J, Silverberg P A, Foster R J, Hyman A I, Millic-Emili J, Kinney J M (1980). Effects of respiratory apparatus on breathing pattern. *J Appl Physiol*; 48: 577-580.
- Atlan G, Bydlowski R, Hatzfield C, Brille D (1968). Etude des variations des gaz du sang artériel au cours du nycthemere chez les insuffisants respiratoires chroniques. *Pathol Biol*; 16: 61-66.
- Aurelianus Caelius (1709). In: *De Morbis Acutis et Chronicis*, Lib 3, Amsterdam.
- Baker R J, Nelder J A (1978). The GLIM system manual. Numerical Algorithms Group, Oxford.
- Barnes P, Fitzgerald G, Brown M, Dollery C (1980). Nocturnal asthma and changes in circulating epinephrine, histamine, and cortisol. *N Engl J Med*; 303: 263-267.
- Barnes P J, Greening A P, Neville L, Timmers J, Poole G W (1982). Single-dose slow-release aminophylline at night prevents nocturnal asthma. *Lancet*; 1: 299-301.
- Barnes P J (1984). Nocturnal asthma: mechanisms and treatment. *Br Med J*; 288: 1397-1398.

- Bateman J R M, Pavia D, Clarke S W (1978). The retention of lung secretions during the night in normal subjects. *Clin Sci*; 55: 523-527.
- Bateman J R M, Clarke S W (1979). Sudden death in asthma. *Thorax*; 34: 40-44.
- Batten J (1978). Diseases of the respiratory system. In: Scott, Sir Ronald Bodley, ed., *Price's textbook of the practice of medicine*, 12th edition. Oxford; Oxford University Press, p 891.
- Baust W, Bohnert B (1977). The regulation of heart rate during sleep. *Exp Brain Res*; 7: 169-180.
- Becker A B, Simons K J, Gillespie C A, Simons F E R (1984). The bronchodilator effects and pharmacokinetics of caffeine in asthma. *N Engl J Med*; 310: 743-746.
- Berthon-Jones M, Sullivan C E (1982). Ventilatory and arousal responses to hypoxia in sleeping humans. *Am Rev Resp Dis*; 125: 632-639.
- Berthon-Jones M, Sullivan C E (1984). Ventilation and arousal responses to hypercapnia in normal sleeping adults. *J Appl Physiol*; 57: 59-67.
- Beumer H M (1979). Bronchial reactivity in asthma to inhaled histamine during treatment with ketotifen. *Respiration*; 37: 271-277.
- Birchfield R I, Sieker H O, Heyman A (1958). Alterations in respiratory function during natural sleep. *J Lab Clin Med*; 54: 216-222.
- Bixler E A, Kales A, Cadieux E J, Vela-Bueno A, Jacoby J A, Soldators C R (1985). Sleep apneic activity in older healthy subjects. *J Appl Physiol*; 58: 1597-1601.
- Block A J, Boysen P G, Wynne J W, Hunt L A (1979). Sleep apnea, hypopnea and oxygen desaturation in normal subjects. A strong male predominance. *N Engl J Med*; 300: 513-517.
- Block A J (1986). Breathing and oxygenation during sleep in normal men and women. *Am Rev Resp Dis*; 133: 506 (letter).
- Bowes G V, Woolf G M, Sullivan C E, Phillipson E A (1980). Effect of sleep fragmentation on ventilatory and arousal responses of sleeping dogs to respiratory stimuli. *Am Rev Resp Dis*; 122: 899-908.
- Boysen P G, Block A J, Wynne J W, Hunt L A, Flick M R (1979). Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Chest*; 76: 536-542.

Bradley C A, Fleetham J A, Anthonisen N R (1979). Ventilatory control in patients with hypoxemia due to obstructive lung disease. *Am Rev Resp Dis*; 120: 21-30.

Bree R (1797). *A Practical Inquiry into Disordered Respiration, Distinguishing the Species of Convulsive Asthma, their Courses and Indications of Cure*. 4th edition, Phillips, London.

Brezinova V, Catterall J R, Douglas N J, Calverley P M A, Flenley D C (1982). Night sleep of patients with chronic ventilatory failure and age matched controls: the number and duration of the EEG episodes of intervening wakefulness and drowsiness. *Sleep*; 5: 123-130.

British Medical Journal (1972). Barbiturates in asthma. Editorial; 3: 490.

British Thoracic Association (1982). Death from asthma in two regions of England. *Br Med J*; 285: 1251-1255.

Browman C P, Sampson M G, Yolles S F, Gujavarty K S, Weiler S J, Walsleben J A, Hahn P M, Mitler M M (1984). Obstructive sleep apnea and body weight. *Chest*; 85: 435-436.

Brownell L G, West P, Sweatman P, Acres J C, Kryger M H (1982). Protryptiline in obstructive sleep apnea: a double blind trial. *N Engl J Med*; 307: 1037-1042.

Brownell L G, West P, Kryger M H (1986). Breathing during sleep in normal pregnant women. *Am Rev Resp Dis*; 133: 38-41.

Bruderman I, Cohen-Aronovski R, Smorzik J (1983). A comparative study of various combinations of ipratropium bromide and metaproteronol in allergic asthmatic patients. *Chest*; 83: 208-210.

Bryan M H (1979). The work of breathing during sleep in newborns. *Am Rev Resp Dis*; 119 supplement: 137-138.

Bulow K (1963). Respiration and wakefulness in man. *Acta Physiol Scand*; 59 (supplement 209): 1-110.

Burney P G J (1986). Asthma mortality in England and Wales: evidence for a further increase. *Lancet*; 2: 323-326.

Burrows B, Niden A H, Fletcher C M, Jones N L (1964). Clinical types of chronic obstructive lung disease in London and Chicago. *Am Rev Resp Dis*; 90: 14-27.

Burwell C S, Robin E D, Whaley R D, Bickelmann A G (1956). Extreme obesity associated with alveolar hypoventilation - A Pickwickian syndrome. *Am J Med*; 21: 811-818.

Bye P T, Issa F, Berthon-Jones M, Sullivan C E (1984). Studies of oxygenation during sleep in patients with interstitial lung disease. *Am Rev Resp Dis*; 129: 27.

Calverley P M A, Brezinova V, Douglas N J, Catterall J R, Flenley D C (1982). The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. *Am Rev Resp Dis*; 126: 206-210.

Calverley P M A, Robson R H, Wraith P K, Prescott L F, Flenley D C (1983). The ventilatory effects of doxapram in normal man. *Clinical Science*; 65: 65-69.

Carpentiere G, Marino S, Castello F (1983). Effects of inhaled fenoterol on the circadium rhythm of expiratory flow in allergic bronchial asthma. *Chest*; 83: 211-214.

Carskadon M A, Dement W C (1981). Respiration during sleep in the aged human. *J Gerontol*; 36: 420-423.

Catterall J R, Douglas N J, Calverley P M A, Shapiro C M, Brezinova V, Brash H M, Flenley D C (1983a). Transient hypoxemia during sleep in chronic obstructive pulmonary disease is not a sleep apnea syndrome. *Am Rev Resp Dis*; 128: 24-29.

Catterall J R, Calverley P M A, Power J T, Shapiro C M, Douglas N J, Flenley D C (1983b). Ketotifen and nocturnal asthma. *Thorax*; 38: 845-848.

Catterall J R, Douglas N J, Calverley P M A, Shapiro C M, Flenley D C (1983c). Transient hypoxaemia during sleep in patients with right-to-left cardiovascular shunts. *Thorax*; 38: 344-348.

Catterall J R, Calverley P M A, Shapiro C M, Ewing D J, Clarke B F, Douglas N J (1984). Breathing, sleep and diabetic autonomic neuropathy. *Diabetes*; 33: 1025-1027.

Catterall J R, Calverley P M A, MacNee W, Warren P M, Shapiro C M, Douglas N J, Flenley D C (1985). Mechanism of transient nocturnal hypoxemia in hypoxic chronic bronchitis and emphysema. *Journal of Applied Physiology* 59: 1698-1703.

Chai H, Farr R S, Frohlich L A, Matheson D A, McLean J A, Rosenthal R R, Sheffer A C, Spector S L, Townley R G (1975). Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol*; 56: 323-327.

Chaudhary B A, Burki N K (1978). Ear oximetry in clinical practice. *Am Rev Resp Dis*; 117: 173-175.

Chen W Y, Chai H (1982). Airway cooling and nocturnal asthma. *Chest*; 81: 675-680.

Cherniack N S (1981). Respiratory dysrhythmias during sleep. *N Engl J Med*; 305: 325-330.

Clark R W, Schmidt H S, Schaal S F et al (1979). Sleep apnea: treatment with protryptiline. *Neurology*; 29: 1287-1292.



- Clark T J H, Collins J V, Tong D (1971). Respiratory depression caused by nitrazepam in patients with respiratory failure. *Lancet*; 2: 737-738.
- Clark T J H, Hetzel M R (1977). Diurnal variation of asthma. *Br J Dis Chest*; 71: 87-92.
- Coccagna G, Mantovani M, Brignani F, Parchi C, Lugaresi E (1972). Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnolence with periodic breathing. *Bull Physiopathol Respir*; 8: 1159-1172.
- Coccagna G, Lugaresi E (1978). Arterial blood gases and pulmonary and systemic arterial blood pressure during sleep in chronic obstructive pulmonary disease. *Sleep*; 1: 117-124.
- Cochrane G M, Clark T J H (1975). A survey of asthma mortality in patients between ages 35 and 64 in the Greater London hospitals in 1971. *Thorax*; 30: 300-305.
- Coe C I, Barnes P J (1986). Reduction of nocturnal asthma by an inhaled anticholinergic drug. *Chest*; 90: 485-488.
- Coleman R M, Roffwarg H P, Kennedy S J (1982). Sleep-wake disorders based on a polysomnographic diagnosis. A national cooperative study. *J Am Med Assoc*; 247: 997-1003.
- Collins D D, Scoggins C G, Zwillich C W, Weil J V (1978). Hereditary aspects of decreased hypoxic responses. *J Clin Invest*; 62: 105-110.
- Connaughton J J, Douglas N J, Morgan A D, Shapiro C M, Critchley J A J H, Pauly N, Flenley D C (1985). Almitrine improves oxygenation when both awake and asleep in patients with hypoxia and carbon dioxide retention caused by chronic bronchitis and emphysema. *Am Rev Resp Dis*; 132: 206-210.
- Connolly C K (1977). Diurnal rhythms in airway obstruction. *Thorax*; 32: 644 (abstract).
- Connolly C K (1979). Diurnal rhythms in airway obstruction. *British Journal of Diseases of the Chest*; 73: 357-366.
- Connolly C K (1981). The effect of bronchodilators on diurnal rhythms in airway obstruction. *Br J Dis Chest*; 75: 197-203.
- Conway W A, Zorick F, Piccione P et al (1982). Protryptiline in the treatment of sleep apnea. *Thorax*; 37: 49-53.
- Cooper K R, Phillips B A (1982). Effect of short-term sleep loss on breathing. *J Appl Physiol*; 53: 855-858.
- Cotes J E (1975). Lung function. Assessment and application in medicine. Third edition, Oxford, Blackwell.

- Cox I D, Hughes D T D, McDonnell K A (1984). Ipratropium bromide in patients with nocturnal asthma. *Postgrad Med J*; 60: 526-538.
- Craps L (1981). Ketotifen in the oral prophylaxis of bronchial asthma: a review. *Pharmatherapeutica*; 3: 18-35.
- Cullen W C (1784) in *First lines of the practice of physic* (Translated Thompson, 1808). 4th edition, Volume III, Book III, Section II, Elliot, Edinburgh and Cadell, London.
- Cummiskey J, Lynne-Davies P, Guilleminault C (1978). Sleep study and respiratory function in myotonic dystrophy. In: Guilleminault C, Dement W C, eds. *Sleep apnoea syndromes*. New York: Liss, 195-308.
- Da Prada M, Zurcher G (1975). Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine in the femtomole range. *Life Science*; 19: 1151-1174.
- Dahlgreen K (1981). Adjustment of circadian rhythms and EEG sleep functions to day and night sleep amongst permanent nightworkers and rotating shiftworkers. *Psychophysiology*; 18: 381-391.
- Davies P D O, Fennerty A G, Benfield G F A, Parrish R W, Campbell I A (1984). Twice daily slow-release theophylline versus placebo for "morning dipping" in asthma. *Br J Clin Pharmacol*; 17: 335-340.
- Davis R S, Larsen G L, Grunstein M M (1983). Respiratory response to intraesophageal acid infusion in asthmatic children during sleep. *J Allergy Clin Immunol*; 72: 393-398.
- Dawkins K D, Muers M F (1981). Diurnal variation in airflow obstruction in chronic bronchitis. *Thorax*, 36: 618-621.
- Deckers W (1975). The chemistry of new derivatives of tropane alkaloids and the pharmacokinetics of a new quaternary compound. *Postgrad Med J*; 51 (supplement 7): 76-81.
- Despas P J, Leroux M, Macklem P T (1972). Site of airway obstruction in asthma as determined by measuring maximal expiratory flow breathing air and a helium-oxygen mixture. *J Clin Invest*; 51: 3235-3243.
- de Vries K, Gori J T, Booy-Noord H, Orie N G M (1962). Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy*; 20: 93-101.
- Documenta Geigy (1970). *Scientific tables*, 6th ed. Basle: J R Geigy S A.
- Dolly F R, Block A J (1980). Medroxyprogesterone acetate and COPD. Effect on breathing and oxygenation in sleeping and awake patients. *Chest*; 84: 394-398.



Dolly F R, Block A J (1982). Increased ventricular ectopy and sleep apnea following ethanol ingestion in COPD patients. *Chest*; 83: 469-472.

Dornhorst A C (1955). Respiratory insufficiency. *Lancet*; 1: 1185-1187.

Douglas N J, Calverley P M A, Leggett R J E, Brash H M, Flenley D C, Brezinova V (1979a). Transient hypoxaemia during sleep in chronic bronchitis and emphysema. *Lancet*; 1: 1-4.

Douglas N J, Brash H M, Wraith P K, Calverley P M A, Leggett R J E, McElderry L E, Flenley D C (1979b). Accuracy, sensitivity to carboxyhaemoglobin and speed of response of the Hewlett-Packard 47201 A ear oximeter. *Am Rev Resp Dis*; 119: 311-313.

Douglas N J, Sudlow M F, Flenley D C (1979c). The effect of an inhaled atropine-like agent on normal airway function. *J Appl Physiol*; 46: 256-262.

Douglas N J, Davidson I, Sudlow M F, Flenley D C (1979). Bronchodilatation and the site of airway resistance in severe chronic bronchitis. *Thorax*; 34: 51-56.

Douglas N J, White C P, Pickett C K, Weil J V, Zwillich C W (1982a). Respiration during sleep in normal man. *Thorax*; 37: 840-842.

Douglas N J, White D P, Weil J V, Pickett C K, Martin R J, Hudgel D W, Zwillich C W (1982b). Hypoxic ventilatory response decreases during sleep in normal men. *Am Rev Resp Dis*; 126: 286-289.

Douglas N J, White D P, Weil J V, Pickett C K, Zwillich C W (1982c). Hypercapnic ventilatory response in sleeping adults. *Am Rev Resp Dis*; 126: 758-762.

Douglas N J (1982d). Breathing during sleep: studies in normal subjects and patients with chronic bronchitis and emphysema. M D Thesis, University of Edinburgh.

Douglas N J (1985). Asthma at night. *Clinics in Chest Medicine*; 6: 663-674.

Doust J W L, Schneider R A (1952). Studies on the physiology of awareness: anoxia and the levels of sleep. *Br Med J*; 1: 449-455.

Drachman D B, Gumnit R J (1962). Periodic alteration of consciousness in the 'Pickwickian' syndrome. *Arch Neurol*; 6: 471-477.

Draper N R, Smith H (1980). Applied regression analysis. 2nd edition. New York: Wiley.

Duron B (1972). Respiratory function during physiological sleep. *Bull Eur Physiopathol Respir*; 8: 1031-1057.

- Dyson A J, Mackay A D (1980). Ketotifen in adult asthma. *Br Med J*; 280: 360-361.
- Edelman N H, Lahiri S, Braudo L, Cherniack N S, Fishman A P (1970). The blunted ventilatory response to hypoxia in cyanotic congenital heart disease. *N Engl J Med*; 282: 405-411.
- Elliot J (1978). Obstructive sleep apnoea in a Georgia family: is it hereditary? *JAMA*; 240: 2611.
- Elwood R K, Abboud R T (1982). The short-term bronchodilator effects of fenoterol and ipratropium in asthma. *J Allergy Clin Immunol*; 69: 467-473.
- Fairfax A J, McNabb W R, Davies H J, Spiro S G (1980). Slow-release oral salbutamol and aminophylline in nocturnal asthma: relation of overnight changes in lung function and plasma drug levels. *Thorax*; 35: 526-530.
- Fairfax A J (1984). The role of beta-adrenoceptor agonists in the treatment of nocturnal asthma. *Royal Society of Medicine International Congress and Symposium Series*; 73: 89-100.
- Fielding J W (1975). "Ondine's curse". A complication of upper cervical-spine surgery. *J Bone Joint Surg*; 57: 1000-1001.
- Fleetham J A, Mezon B, West P, Bradley C A, Athonisen N R, Kryger M H (1980). Chemical control of ventilation and sleep arterial oxygen desaturation in patients with COPD. *Am Rev Resp Dis*; 122: 583-589.
- Fleetham J, West P, Mezon B, Conway W, Roth T, Kryger M (1982). Sleep, arousals, and oxygen desaturation in chronic obstructive pulmonary disease. The effect of oxygen therapy. *Am Rev Resp Dis*; 126: 429-433.
- Fleetham J A, Fera T, Edgell G, Jamal K (1983). The effect of theophylline therapy on sleep disorders in COPD patients. *Am Rev Resp Dis*; 127 (supplement): 85 (abstract).
- Flenley D C, Millar J S (1967). Ventilatory response to oxygen and carbon dioxide in chronic respiratory failure. *Clinical Science*; 33: 319-334.
- Flenley D C, Franklin D H, Millar J S (1970). The hypoxic drive to breathing in chronic bronchitis and emphysema. *Clinical Science*; 38: 503-518.
- Flenley D C (1978). Clinical hypoxia: causes, consequences, and correction. *Lancet*; 1: 542-546.
- Flenley D C (1985). Sleep in chronic obstructive lung disease. *Clinics in Chest Medicine*; 6: 65-661.

- Fletcher E C, Gray B A, Levin D C (1983). Nonapneic mechanism of arterial oxygen desaturation during rapid-eye-movement sleep. *J Appl Physiol*; 54: 632-639.
- Fletcher E C, Levin D C (1984). Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. *Chest*; 85: 6-14.
- Fletcher E C, De Behnke R D, Lovoi M S, Gorin A B (1985). Undiagnosed sleep apnea in patients with essential hypertension. *Ann Intern Med*; 103: 190-195.
- Flick M R, Block A J (1977). Continuous in-vivo monitoring of arterial oxygen saturation in chronic obstructive lung disease. *Ann Intern Med*; 86: 725-730.
- Flick M R, Block A J (1979). Nocturnal vs diurnal arrhythmias in patients with chronic obstructive pulmonary disease. *Chest*; 75: 8-11.
- Floyer J (1689). A treatise of the asthma. Wilkin and Innys, London.
- Fraser P, Doll R (1971). Geographical variations in the epidemic of asthma deaths. *Brit J Prev Soc Med*; 25: 34-36.
- Fraser R G, Parre J A P (1979). Diagnosis of diseases of the chest, volume III, 2nd edition. Saunders, Philadelphia, p 1345.
- Fruhmann G (1972). Hypersomnia with primary hypoventilation syndrome and following cor pulmonale (Ondine's Curse Syndrome). *Bull Physiopathol Respir*; 8: 1173-1179.
- Gaddie J, Legge J S, Palmer K N V, Petrie J S, Wood R A (1972). Effect of nitrazepam in chronic obstructive bronchitis. *Br Med J*; 2: 688-690.
- Gaultier C, Reinberg A, Girard F (1977). Circadian rhythms in lung resistance and dynamic lung compliance. *Respiration Physiology*; 31: 169-182.
- Gastaut H, Tassinari C A, Duron B (1975). Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwick Syndrome. *Brain Res*; 1: 167-186.
- Gilbert R, Auchincloss J H, Brodsky J, Boden W (1972). Changes in tidal volume, frequency and ventilation induced by their measurement. *J Appl Physiol*; 33: 252-254.
- Gobel P (1978). The protective effect of ketotifen in bronchial asthma. *J Int Med Res*; 6: 79-85.
- Goldie L, Green J M (1961). Changes in mode of respiration as an indication of level of awareness. *Nature*; 189: 581-582.

Goldstein R S, Ramcharan V, Bowes G, McNicholas W T, Bradley D, Phillipson E A (1984). Effect of supplemental nocturnal oxygen on gas exchange in patients with severe obstructive lung disease. *N Engl J Med*; 310: 425-429.

Gothé B, Goldman M D, Cherniack N S, Mantey P (1982). Effect of progressive hypoxia on breathing during sleep. *Am Rev Resp Dis*; 126: 97-102.

Gould G, Rhind G B, Whyte K F, Macfie J, Catterall J R, Douglas N J (1986). The sleep hypopnoea syndrome. *Am Rev Resp Dis*; 133: A234 (abstract).

Gross N J (1975). Sch 1000: a new anticholinergic bronchodilator. *Am Rev Resp Dis*; 112: 823-828.

Gross N J, Skorodin M S (1984). Anticholinergic antimuscarinic bronchodilators. *Am Rev Resp Dis*; 129: 856-870.

Guberan E, William M K, Walford J, Smith M M (1969). Circadian variation of FEV<sub>1</sub> in shift workers. *Br Journal of Industrial Medicine*; 26: 121.

Guilleminault C, Eldridge F L, Dement W C (1973). Insomnia with sleep apnea: a new syndrome. *Science*; 181: 856-858.

Guilleminault C, Tilkian A, Dement W C (1976). The sleep apnea syndromes. *Ann Rev Medicine*; 27: 465-484.

Guilleminault C, van den Hoed J, Mitler M M (1978). Clinical overview of the sleep apnea syndromes. In: Guilleminault C, Dement W C, ed. *Sleep apnea syndromes*. New York: Liss 1-12.

Guilleminault C (1980). Sleep apnea syndromes: impact of sleep and sleep states. *Sleep*; 3: 227-234.

Guilleminault C, Cumiskey J, Motta J (1980a). Chronic obstructive airflow disease and sleep studies. *Am Rev Resp Dis*; 122: 397-406.

Guilleminault C, Cumiskey J, Dement W C (1980b). Sleep apnea syndrome: recent advances. *Adv Intern Med*; 26: 347-372.

Guilleminault C, Kurland G, Winkle R, Miles L E (1981a). Severe kyphoscoliosis, breathing and sleep. The "Quasimodo" syndrome during sleep. *Chest*; 79: 626-630.

Guilleminault C, Simmons F B, Motta J, Cumiskey J, Rosekind M, Schroeder J S, Dement W C (1981b). Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. *Arch Intern Med*; 141: 985-988.

Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A (1984). Cyclical variation of the heart rate in sleep apnoea syndrome. *Lancet*; 1: 126-131.

- Guilleminault C, Heldt G, Powell N, Riley R (1986). Small upper airway in near-miss sudden infant death syndrome: infants and their families. *Lancet*; 1: 402-407.
- Hagan R, Bryan A C, Bryan M H, Gulston G (1977). Neonatal chest wall afferents and regulation of respiration. *J Appl Physiol*; 42: 363-367.
- Harman E, Wynne J W, Block A J, Malloy-Fisher I (1981). Sleep disordered breathing and oxygen desaturation in obese subjects. *Chest*; 79: 256-260.
- Harvey S C (1975). Hypnotics and sedatives. In: Goodman L S, Gillman A, eds. *The pharmacological basis of therapeutics*. 5th ed. New York: Macmillan: 134.
- Hedemark L L, Kronenberg R S (1982). Ventilatory and heart rate responses to hypoxia and hypercapnia during sleep in adults. *J Appl Physiol*; 53: 307-312.
- Henderson-Smart D J, Read D J C (1978). Depression of intercostal and abdominal muscle activity and vulnerability to asphyxia during active sleep in the newborn. In: Guilleminault C, Dement W C, eds. *Sleep apnea syndromes*, New York: Liss, 93-117.
- Herzog H (1975). Comparison of anticholinergic agents other than bronchodilators and the effect of combining these drugs. *Postgrad Med J*; 51 (supplement 7): 146-147.
- Hetzel M R, Clark T J H, Branthwaite M A (1977a). Asthma: analysis of sudden deaths and ventilatory arrests in hospital. *Br Med J*; 1: 808-811.
- Hetzel M R, Clark T J H, Houston K (1977b). Physiological patterns in early morning asthma. *Thorax*; 32: 418-423.
- Hetzel M R, Clark T J H (1979). Does sleep cause nocturnal asthma? *Thorax*; 34: 749-754.
- Hetzel M R (1980). Observations on 24 hour periodicity in asthma. M D Thesis, University of London.
- Hetzel M R, Clark T J H (1980). Comparison of normal and asthmatic rhythms in peak expiratory flow rate. *Thorax*; 35: 732-738.
- Hill R, Robbins A W, Messing R, Arora N S (1983). Sleep apnea after poliomyelitis. *Am Rev Resp Dis*; 127: 129-131.
- Hirshman C A, McCullough R E, Weil J V (1975). Normal values for hypoxic and hypercapnic ventilatory drives in man. *J Appl Physiol*; 38: 1095-1098.
- Horn C R, Clark T J H, Cochrane G M (1984). Inhaled therapy reduces morning dips in asthma. *Lancet*; 1: 1143-1145.



Hudgel D W, Devadatta P (1984). Decrease in functional residual capacity during sleep in normal humans. *J Appl Physiol*; 57: 1319-1322.

Hudgel D W, Martin R J, Johnson B, Hill P (1984). Mechanics of the respiratory system and breathing pattern during sleep in normal humans. *J Appl Physiol*; 56: 133-137.

Hughes D M, Spier S, Rivlin J et al (1983). Gastroesophageal reflux during sleep in asthmatic patients. *J Pediatr*; 102: 666-672.

Innouye T, Waters P, Braude A C et al (1984). Gastroesophageal reflux and respiratory symptoms evaluated by 24-hour pH monitoring, bronchoalveolar lavage and peak expiratory flow rate. *Am Rev Resp Dis*; 129, supplement: A40 (abstract).

Interiano B, Perkins P T, Fuleihan F, Summers D S, Hyde R W (1972). Changes in arterial blood gas during sleep in patients with cardiopulmonary disease. *Am Rev Resp Dis*; 105-180 (abstract).

Issa F G, Sullivan C E (1982). Alcohol, snoring and sleep apnea. *J Neurol Neurosurg Psychiatry*; 45: 353-359.

Issa F G, Sullivan C E (1985). Respiratory muscle activity and thoracoabdominal motion during acute episodes of asthma during sleep. *Am Rev Resp Dis*; 132: 999-1004.

Jackson R T, Beaglehole R, Rea H H, Sutherland D C (1982). Asthma mortality: a new epidemic in New Zealand. *Br Med J*; 285: 771-774.

Jacobs M H, Senior R M, Ressler G (1976). Clinical experience with theophylline: relationship between dosage, serum concentration and toxicity. *JAMA*; 235: 1983-1986.

Jaffe J H (1980). Drug addiction and drug abuse. In: Goodman A G, Goodman I S, Gilman L S, eds. *The pharmacological basis of therapeutics*, sixth edition, New York, Macmillan.

Johnston I D A, Anderson H R, Patel S (1984). Variability of peak flow in wheezy children. *Thorax*; 39: 583-587.

Kader G A, Griffin P T (1983). Re-evaluation of the phenomena of the first night effect. *Sleep*; 6: 67-71.

Kales A, Beall G N, Bajor G F, Jacobson A, Kales J D (1968). Sleep studies in asthmatic adults: relationship of attacks to sleep stage and time of night. *J Allergy*; 41: 164-173.

Kales A, Kales J D, Sly R M, Scharf M B, Tan T L, Preston T A (1970). Sleep patterns of asthmatic children: all night electroencephalographic studies. *J Allergy*, 46: 300-308.

Kales A, Bixler E O, Cadieux R J, Scheck D W, Shaw L C, Locke T W, Vela-Bueno A, Soldatos C R (1984). Sleep apnoea in a hypertensive population. *Lancet*; 2: 1005-1008.

Kepron W, Cherniack R M (1973). The ventilatory response to hypercapnia and to hypoxemia in chronic obstructive lung disease. *Am Rev Resp Dis*; 108: 843-850.

Kerin N Z, Edelstein J, Goldberg L B, Louridas G (1979). Cardiac dysrhythmias associated with obesity and sleep apnea. *Cardiovascular Med*; 4: 1167-1174.

Kerr H D (1973). Diurnal variation of respiratory function independent of air quality. *Archives of Environmental Health*; 26: 144-152.

Kono K, Mead J (1967). Measurement of the separate volume changes of rib cage and abdomen during breathing. *J Appl Physiol*; 22: 407-422.

Koo K W, Sax D S, Snider G L (1975). Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. *Am J Med*; 58: 663-670.

Kramer K (1935). Ein verfahren zur fortlaufenden, messung des sauerstoffgehaltes im stromenden blute an uneroffheten gefassen. *Z Bio*, 96, 61. Cited in Burki N K, Albert R K (1983). Noninvasive monitoring of arterial blood gases. *Chest*; 83: 666-670.

Kreider M B, Buskirk E R, Bass D E (1958). Oxygen consumption and body temperatures during the night. *J Appl Physiol*; 12: 361-366.

Kreiger A J (1978). Sleep apnea produced by cervical cordotomy and other neurosurgical lesions in man. In: Guilleminault C, Dement W C, eds. *Sleep apnea syndromes*. New York: Liss.

Krieger J, Kurtz D (1983a). Effects of pneumotachygraphic recordings of breathing on sleep and respiration during sleep. *Bull Eur Physiopathol Respir*; 19: 641-644.

Krieger J, Turlot J, Mangin P, Kurtz D (1983b). Breathing during sleep in normal young and elderly subjects: hypopneas, apneas, and correlated factors. *Sleep*; 6: 108-120.

Krieger J (1985). Breathing during sleep in normal subjects. *Clinics in Chest Medicine*; 6: 577-594.

Kryger M H, Glas R, Jackson D, McCullough R E, Scoggin C, Grover R F, Weil J V (1978). Impaired oxygenation during sleep in excessive polycythemia of high altitude: improvement with respiratory stimulation. *Sleep*; 1: 3-17.

Kryger M H (1985), ed. *Symposium on sleep disorders*. *Clinics in Chest Medicine*, vol 6; no 4.

Laennec R T J (1819). A treatise on the diseases of the chest and on mediate auscultation. Translated by John Forbes. In: Willins F A, Keys T E, eds (1941). *Cardiac classics*. London: Kimpton.

Laennec R T H (1827). A treatise on the diseases of the chest and on mediate auscultation (Translated, Forbes), Underwood, London.

Lancet (1983). Asthma at night. Editorial; 1: 220-222.

Larsson S, Svedmyr N (1977). Bronchodilating effect and side effects of beta<sub>2</sub>-adrenoceptor stimulants by different modes of administration (tablets, metered aerosol, and combinations thereof). A study with salbutamol in asthmatics. Am Rev Resp Dis; 116: 861-869.

Lavie P (1983). Incidence of sleep apnea in a presumably healthy working population: a significant relationship with excessive daytime sleepiness. Sleep; 6: 312-318.

Lavie P, Ben-Yosef R, Rubin A E (1984). Prevalence of sleep apnea syndrome among patients with essential hypertension. Am Heart J; 108: 373-376.

Lefcoe N M, Toogood J H, Blennerhassett G, Baskerville J, Patterson N A M (1982). The addition of an aerosol anticholinergic to an oral beta agonist plus theophylline in asthma and bronchitis. Chest; 82: 300-305.

Leitch A G, Clancy L J, Leggett R J E, Tweeddale P, Dawson P, Evans J I (1976). Arterial blood gas tensions, hydrogen ion, and electroencephalogram during sleep in patients with chronic ventilatory failure. Thorax; 31: 730-735.

Lewinsohn H C, Capel L H, Smart J (1960). Changes in forced expiratory volumes throughout the day. Br Med J; 1: 462-464.

Lightbody I M, Ingram C G, Legge J S, Johnston R N (1978). Ipratropium bromide, salbutamol and prednisolone in bronchial asthma and chronic bronchitis. Br J Dis Chest; 72: 181-186.

Lisboa C, Moreno R, Cruz E, Barja S, Sanchez I, Moran J, Ferrett R (1985). Acute effect of ketotifen on the dose - response curve of histamine and methacholine in asthma. Br J Dis Chest; 79: 235-243.

Lloyd B B, Jukes M G M, Cunningham D J C (1958). The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Quart J Exp Physiol; 43: 214-226.

Lugaresi E (1968). La "maledizione di Ondine" il disturbo del respiro e del sonno nell ipoventilazione alveolare primaria. Sist Nerv; 20: 27-37.

Lopata M, Onal E (1982). Mass loading, sleep apnea, and the pathogenesis of obesity hypoventilation. Am Rev Resp Dis; 126: 640-645.



Lopes J M, Tabachnik E, Muller N L (1983). Total airway resistance and respiratory muscle activity during sleep. *J Appl Physiol*; 54: 773-777.

McDermott W (1966). Diurnal and weekly cyclical changes in lung airways resistance. *Journal of Physiology*; 186: 90P (abstract).

MacDonald J B, Seaton A, Williams D A (1976a). Asthma deaths in Cardiff 1963-74: 90 deaths outside hospital. *Br Med J*; i: 1493-1495.

MacDonald J B, MacDonald E T, Seaton A, Williams D A (1976b). Asthma deaths in Cardiff 1963-74: 53 deaths in hospital. *Br Med J*; ii: 721-723.

McFadden E R, Lyons H A (1968). Arterial blood gas tensions in asthma. *N Engl J Med*; 278: 1027-1032.

McFadden E R, Jr (1986). Clinical appraisal of the therapy of asthma. *Am Rev Resp Dis*; 133: 723-724.

McNicholas W T (1986). Sleep apnoea in the British Isles. *Lancet*; 2: 295.

Magnussen G (1944). Studies on the respiration during sleep. A contribution to the physiology of the sleep function. London: Lewis.

Maimonides M (12th century). Treatise on asthma. Translated and edited by S Muntner (1963). The medical writings of Moses Maimonides. Lippincot, Philadelphia.

Major R H (1953). A note on the history of asthma. In: Underwood E A, ed. Science, Medicine and History. Oxford University Press, London.

Mak H, Chipps B E, Mankes H A, Schuberth K C, Talamo J H, Scherr K S, Talamo R C, Permutt S (1982). Diurnal variation of air and helium-oxygen flow volume curves in asthmatic children. *Br J Dis Chest*; 76: 51-56.

Mannix S E, Chowienzyk P, Barnes P J (1984). New device for airflow measurement: comparison with pneumotachograph and differentiated respiration volume. *Clin Sci*; 66: 58P.

Martin M E, Grunstein M M, Larsen G L (1982). The relationship of gastroesophageal reflux to nocturnal wheezing in children with asthma. *Ann Allergy*; 49: 318-322.

Martin R J, Block A J, Cohn M A, Conway W A, Hudgel D W, Powles A C P, Sanders M H, Smith P L (1985). Indications and standards for cardiopulmonary sleep studies. *Sleep*; 8: 371-379.

Martin V, Romer D (1978). The pharmacological properties of a new orally active antianaphylactic compound. *Arzneim Forsch*; 28: 770-782.

Matthes K (1935). Untersuchungen über die sauerstoff sättigung des arterienbluts. *Arch Exp Pathol Pharmacol*; 179: 698. Cited in Burki N I, Albert R K (1983). Noninvasive monitoring of arterial blood gases. *Chest*; 83: 666-670.

Matthews A W. The relationship between central carbon dioxide sensitivity and clinical features in patients with chronic airways obstruction. *Quart J Med*; 182: 179-195.

Mattson K, Poppius H, Nikander-Hurme R (1979). Preventive effect of ketotifen, a new antiallergic agent, on histamine-induced bronchoconstriction in asthmatics. *Clin Allergy*; 9: 411-416.

Mead J, Peterson N, Grimby G, Mead J (1967). Pulmonary ventilation measured from body surface movements. *Science*; 156: 1383-1384.

Medical Research Council (1965). Definition and classification of chronic bronchitis. *Lancet*; 1: 775-779.

Medical Research Council Working Party (1981). Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet*; 1: 681-686.

Mendels J, Dawkins D R (1967). Sleep laboratory adaptation in normal subjects and depressed patients, first night effect. *Electroencephalogr Clin Neurophysiol*; 22: 556-558.

Mendelson W B, Garnett D, Gillin J C (1981). Flurazepam-induced sleep apnea syndrome in a patient with insomnia and mild sleep related respiratory changes. *J Nerv Ment Dis*; 169: 261-264.

Mezon B L, West P, Israels J, Kryger M (1980). Sleep breathing abnormalities in kyphoscoliosis. *Am Rev Resp Dis*; 122: 617-621.

Milledge J S, Lahiri S (1967). Respiratory control in lowlanders and in Sherpa highlanders at altitude. *Respir Physiol*; 2: 310-322.

Milledge J S, Stott F D (1977). Inductive plethysmography - a new respiratory transducer. *J Physiol (London)*; 267: 4P-5P (abstract).

Milledge J S, Morris J (1979). A comparison of slow-release salbutamol with slow-release aminophylline in nocturnal asthma. *J Int Med Res*; 7 (supplement 1): 106-110.

Millikan G A (1942). The oximeter, an instrument for measuring continuously the oxygen saturation of arterial blood in man. *Rev Sci Instrum*; 13: 434-444.

Monie R D, Smith A P, Leopold D, Anderson G, Davies B H, Thomas G O (1982). A double-blind clinical trial of ketotifen and disodium cromoglycate in bronchial asthma. *Br J Dis Chest*; 76: 383-389.

Montplaisir J, Walsh J, Malo J L (1982). Nocturnal asthma: features of attacks, sleep and breathing patterns. *Am Rev Resp Dis*; 125: 18-22.

Moore-Gillon J C, Cameron I R (1985). Right ventricular hypertrophy and polycythaemia in rats after intermittent exposure to hypoxia. *Clin Sci*; 69: 595-599.

Morgan A D, Rhind G B, Connaughton J J, Flenley D C (1986). Breathing and oxygenation during sleep in patients with asthma. Submitted for publication.

Mortola J P, Anch A M (1978). Chest wall configuration in supine man: wakefulness and sleep. *Respir Physiol*; 35: 201-213.

Mosso A (1878). Ueber die gegenseitigen beziehungen der bauchund brustathmung. *Arch Anat (Leipzig): Physiol*: 441-468.

Mountain R, Zwillich C, Weil J (1978). Hypoventilation in obstructive lung disease. The role of familial factors. *N Engl J Med*; 298: 521-525.

Muller N L, Francis P W, Gurwitz D, Levison H, Bryan A C (1980). Mechanism of hemoglobin desaturation during rapid-eye-movement sleep in normal subjects and in patients with cystic fibrosis. *Am Rev Resp Dis*; 121: 463-469.

Neagley S R, White D P, Zwillich C W (1986). Does disordered breathing during sleep occur in stable asthmatics? *Am Rev Resp Dis*; 133 (supplement): A180 (abstract).

Neubauer J A, Santiago T V, Edelman N H (1981). Hypoxic arousal in the intact and carotid chemodenervated sleeping cat. *J Appl Physiol*; 51: 1294-1299.

Nocturnal Oxygen Therapy Trial Group (1980). Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Ann Intern Med*; 93: 391-398.

Office of Population Censuses and Surveys. Mortality statistics - cause. England and Wales 1974-1984. Series DH2. London: HMSO, annual.

O'Flaherty J J, Sant'Ambrogio G, Mognoni P, Saiebene F, Camporesi E (1973). Ribcage and abdomen-diaphragm contribution to ventilation during sleep in man. *Arch Fisiol*; 70: 78-80.

Onal E, Lopata M, O'Connor T (1982). Pathogenesis of apneas in hypersomnia-sleep apnea syndrome. *Am Rev Resp Dis*; 125: 167-174.

Onions C T (1966). *The Oxford Dictionary of English Etymology*: Oxford University Press.

Ostergaard T (1944). The excitability of the respiratory centre during sleep and during lirrpan anaesthesia. *Acta Physiol Scand*; 8: 1-15.

Peiser J, Lavie P, Ovnat A, Charuzi I (1984). Sleep apnea syndrome in the morbidly obese as an indication for weight reduction surgery. *Ann Surgery*; 199: 112-115.

Pepys J, Davies R J (1977). Allergy. In: Clark T J H and Godfrey S, eds. *Asthma*, London: Chapman and Hall.

Perez-Padilla R, West P, Lertzman M (1985). Breathing during sleep in patients with interstitial lung disease. *Am Rev Resp Dis*; 132: 224-229.

Perkoff G T, Eik-nes K, Nugent C A, Fred H L, Nimer R A, Rush L, Samuels L T, Tyler F H (1959). Studies of the diurnal variation of plasma 17-hydroxycorticosteroids in man. *J Clin Endocrinol Metab*; 19: 432-443.

Petheram I S, Moxham J, Berman C W, McAllen M, Spiro S G (1981). Ketotifen in atopic asthma and exercise induced asthma. *Thorax*; 36: 308-312.

Phillipson E A (1978). Respiratory adaptations in sleep. *Ann Rev Physiol*; 40: 133-156.

Phillipson E A, Sullivan C E, Read D J C, Murphy E, Kozar L F (1978). Ventilatory and waking responses to hypoxia in sleeping dogs. *J Appl Physiol*; 44: 512-520.

Pierce A K, Jarret C E, Werkle G, Miller W F (1966). Respiratory function during sleep in patients with chronic obstructive lung disease. *J Clin Invest*; 45: 631-636.

Platts-Mills T A E, Mitchell E B, Nock P, Tovey E R, Moszoro H, Wilkins S R (1982). Reduction of bronchial hyper-reactivity during prolonged allergen avoidance. *Lancet*; 2: 675-677.

Postma D S, Keyzer J J, Koeter G H, Sluiter H J, de Vries K (1985). Influence of parasympathetic and sympathetic nervous system on nocturnal bronchial obstruction. *Clin Sci*; 69: 251-258.

Prinz P N, Vitiello M V, Smallwood R G, Schoene R B, Halter J B (1984). Plasma norepinephrine in normal young and aged men: relationship with sleep. *J Gerontol*; 39: 561-567.

Rall T W (1980). Central nervous system stimulants. The xanthines. In: Goodman A G, Goodman L S, Gilman A, eds. *The pharmacological basis fo therapeutics*, sixth edition. New York; Macmillan, 592-607.

Ravenscroft K, Hartmann E L (1958). The temporal correlation of nocturnal asthmatic attacks in the D stage. *Psychophysiol*; 4: 396-397 (abstract).

Rebuck A F, Read J (1971). Patterns of ventilatory response to carbon dioxide during recovery from severe asthma. *Clinical Science*; 41: 13-21.

Rebuck A S, Chapman K R, D'urzo A (1983). The accuracy and response characteristics of a simplified ear oximeter. *Chest*; 83: 860-864.

Rechtshaffen A, Kales A (1968). A manual of standardised terminology, techniques and scoring system for sleep stages of human subjects. Bethesda, Maryland: National Institute of Neurological Disease and Blindness (NIH publication No 204).

Reed C I, Kleitman N (1926). Effect of sleep on respiration. *Am J Physiol*; 75: 600-608.

Rees A H, Miller J S, Donald K W (1968). A study of the clinical course and arterial blood gas tensions of patients in status asthmaticus. *Quart J Med*; 37 (new series): 541-561.

Registrar General for Scotland. Annual Report 1974-1984. Edinburgh: HMSO, annual.

Reinberg A, Ghata J, Sidi E (1963). Nocturnal asthma attacks: their relationship to the circadian adrenal cycle. *J Allergy*; 34: 323-330.

Reinberg A, Halberg F, Ghata J (1969). Rythme circadien de diverse fonction physiologiques de l'homme adult sain, actif et au repos. *J Physiol (Paris)*; 61 (supplement 2): 383.

Reinberg A, Gervais P, Frambourg J C, Halberg F, Abulker C, Vignaud D, Dupont J (1970). Rythmes circadiens de fonctions respiratoires et de la temperature d'asthmatiques sejourant en millieu hypoallergenique. *La Presse Medicale*; 78: 1817-1821.

Reinberg A, Gervais P (1972). Circadian rhythms in respiratory functions, with special reference to human chronophysiology and chronopharmacology. *Bull Physio-Path Resp*; 8: 663-675.

Reindl K, Falliers C, Halberg F, Chai H, Hillman D, Nelson W (1970). Circadian acrophase in peak expiratory flow rate and urinary electrolyte secretion of asthmatic children. Phase shifting of rhythms by prednisone given in different circadium system phases. *Rassagna di Neurologia Vegetativa*; 23: 5-26.

Reinhardt D, Schuhmacher P, Fox A, Stemman E A, Wegner F (1980). Comparison of the effects of theophylline, prednisolone and sleep withdrawal on airway obstruction and urinary cyclic AMP/cyclic GMP excretion of asthmatic children with and without nocturnal asthma. *Int J Clin Pharmacol Ther Toxicol*; 18: 399-404.

Reissiessen (1822). *Über den bau der lunge*. Berlin.



Remmers J E, de Groot W J, Saverland E K, Anch A M (1978). Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol*; 44: 931-938.

Rhind G B, Connaughton J J, McFie J, Douglas N J, Flenley D C (1985). Sustained release choline theophyllinate in nocturnal asthma. *Br Med J*; 291: 1605-1697.

Ries A L, Farrow J T, Clausen J L (1984). Accuracy of two ear oximeters at rest and during exercise in pulmonary patients. *Am Rev Resp Dis*; 129: A79 (abstract).

Robin E D (1958). Some interrelationships between sleep and disease. *Arch Intern Med*; 102: 669-675.

Robin E D, Whaley R D, Crump C H, Travis D M (1958). Alveolar gas tensions, pulmonary ventilation and blood pH during physiological sleep in normal subjects. *J Clin Invest*; 37: 981-989.

Robin E D, O'Neill R P (1963). The fighter versus the non-fighter. *Arch Environ Health*; 7: 125-129.

Rominger K L (1979). Chemistry and pharmacokinetics of ipratropium bromide. *Scand J Respir Dis*; 103 (supplement): 116-126.

Rossing T H, Fanta C H, Goldstein D H, Snapper J R, McFadden E R Jr (1980). Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetic and infused aminophylline. *Am Rev Resp Dis*; 122: 365-371.

Royal Society of Medicine (1984). Nocturnal asthma. International Congress and Symposium Series; No 73: London.

Ruffin R E, McIntyre E, Crockett A J, Zeilonka K, Alpers J H (1982). Combination bronchodilator therapy in asthma. *J Allergy Clin Immunol*; 69: 60-65.

Ryan G, Latimer K M, Dolovich J, Hargreave F E (1982). Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. *Thorax*; 37: 423-429.

Sackner M A (1980). Monitoring of ventilation without a physical connection to the airway. In: Sackner M A, ed. Diagnostic techniques in pulmonary disease, part 1. New York: Dekker, 503-537.

Salter H (1859). On some points in the treatment and clinical history of asthma. *Edinburgh Medical Journal*; 4: 1109-1115.

Salter H H (1868). On asthma. Its pathology and treatment. 2nd edition, Churchill, London.

Saunders N A, Powles A C P, Rebuck A S (1976). Ear oximetry: accuracy and practicability in the assessment of arterial oxygenation. *Am Rev Res Dis*; 113: 745-749.

Savin J A, Paterson W D, Oswald I (1973). Scratching during sleep. *Lancet*; 2: 296-297.

Schiffman P L, Trontell M C, Mazar M F, Edelman N H (1983). Sleep deprivation decreases ventilatory response to CO<sub>2</sub> but not load compensation. *Chest*; 84: 695-698.

Schmidt H S, Kaelbling R (1971). The differential laboratory adaptation of sleep parameters. *Biol Psychiatry*; 33: 33-45.

Schroeder J S, Motta J, Guilleminault C (1978). Hemodynamic studies in sleep apnea. In: Guilleminault C, Dement W C, eds. *Sleep apnea syndromes*. New York; Liss: 177-196.

Scrima L, Broudy M, Nay K et al (1982). Increased severity of obstructive sleep apnoea after bedtime alcohol ingestion: diagnostic potential and proposed mechanism of action. *Sleep*; 5: 318-328.

Severinghaus J W (1966). Blood gas calculator. *J Appl Physiol*; 21: 1108-1116.

Severinghaus J W, Bainton C R, Carcelen A (1966). Respiratory sensitivity to hypoxia in chronically hypoxic man. *Respir Physiol*; 1: 308-334.

Shapiro C M, Catterall J R, Oswald I, Flenley D C (1982). Where are the British sleep apnoea patients? *Lancet*; 2: 523.

Sharp J T, Goldberg N B, Druz W S, Danon J (1975). Relative contributions of rib cage and abdomen to breathing in normal subjects. *J Appl Physiol*; 39: 608-618.

Sharp J T, Druz W S, Foster J R, Wicks M S, Chokroverty S (1980). Use of the respiratory magnetometer in diagnosis and classification of sleep apnea. *Chest*; 77: 350-353.

Shepard J F (1914). *The circulation and sleep*. New York, Macmillan.

Skatrud J B, Dempsey J A, Kaiser D G (1978). Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism. *J Appl Physiol*; 44: 939-944.

Skatrud J B, Iber C, McHugh H, Rasmussen H, Nichols D (1980). Determinants of hypoventilation during wakefulness and sleep in diaphragmatic paralysis. *Am Rev Res Dis*; 121: 587-593.

Skatrud J B, Dempsey J A, Iber C, Berssenbrugge A (1982). Correction of CO<sub>2</sub> retention during sleep in patients with chronic obstructive pulmonary diseases. *Am Rev Res Dis*; 124: 260-268.

Skatrud J B, Dempsey J A (1985). Airway resistance and respiratory muscle function in snorers during NREM sleep. *J Appl Physiol*; 59: 328-335.

Slutsky A S, Strohl K P (1980). Quantification of oxygen saturation during episodic hypoxemia. *Am Rev Resp Dis*; 121: 893-895.

Smallwood R G, Vitiello M V, GIBLIN E C, Prinz P N (1983). Sleep apnea: relationship to age, sex and Alzheimer's dementia. *Sleep*; 6: 16-22.

Smith E (1860). *Recherches experimentales sur la respiration*. *J Physiol de l'homme et des animaux*; 3: 506-521.

Smith P L, Haponik E F, Allen R P (1983). The effect of protryptiline in sleep disordered breathing. *Am Rev Resp Dis*; 127: 8-13.

Smolensky M, Halberg F, Sargent F (1972). Chronobiology of the life sequence. In: Itoh S, Ogata K, Yoshimura H, eds. *Advances in climatic physiology*. Berlin; Springer Verlag: 281-318.

Snedecor G W, Cochran W G (1980). *Statistical methods*. 7th ed. Iowa: Iowa State University Press.

Snyder F, Hobson J A, Morrison D F, Goldfrank F (1964). Changes in respiration, heart rate and systolic blood pressure in human sleep. *J Appl Physiol*; 19: 417-422.

Sorensen S C, Severinghaus J W (1968). Respiratory insensitivity to acute hypoxia persisting after correction of tetralogy of Fallot. *J Appl Physiol*; 25: 221-223.

Soutar C A, Costello J, Ijaduola O, Turner-Warwick M (1975). Nocturnal and morning asthma. Relationship to plasma corticosteroids and response to cortisol infusion. *Thorax*; 30: 436-440.

Soutar C A, Carruthers M, Pickering C A C (1977). Nocturnal asthma and urinary adrenaline and noradrenaline excretion. *Thorax*; 32: 677-683.

Speizer F E, Doll R, Heaf P (1968a). Observations on recent increase in mortality from asthma. *Br Med J*; 1: 335-339.

Speizer F E, Doll R, Heaf P, Strang L B (1968b). Investigation into use of drugs preceding deaths from asthma. *Br Med J*; 1: 339-343.

Steinschneider A (1972). Prolonged apnea and the sudden infant death syndrome: clinical and laboratory observations. *Pediatrics*; 50: 646-654.

Steriade M, Hobson J A (1976). Neuronal activity during the sleep-waking cycle. *Progr Neurobiol*; 6: 155-376.



Stewart I C, Catterall J R, Wraith P K, Douglas N J, Flenley D C (1984a). Breathing patterns in acute asthma and in bronchoconstriction induced by histamine and methacholine. *Am Rev Resp Dis*; 129 (supplement): A47 (abstract).

Stewart I C, Rhind G B, Power J T, Douglas N J, Flenley D C (1984b). Nocturnal symptoms and sleep in adult asthmatics after terbutaline SA. *Respiration physiology* (supplement 1): 60 (abstract).

Stradling J R, Lane D J (1983). Nocturnal hypoxaemia in chronic obstructive pulmonary disease. *Clin Sci*; 64: 213-222.

Stradling J R, Chadwick G A, Frew J A (1985). Changes in ventilation and its components in normal subjects during sleep. *Thorax*; 40: 364-370.

Strohl K P, Saunders N A, Feldman N T, Hallett M (1978). Obstructive sleep apnea in family members. *N Engl J Med*; 299: 969-973.

Sullivan C E, Zamel N, Kozar L F, Murphy E, Phillipson E A (1979). Regulation of airway smooth muscle tone in sleeping dogs. *Am Rev Resp Dis*; 119: 87-99.

Sullivan C E, Issa F G, Berthon-Jones, Eves L (1981). Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nose. *Lancet*; 1: 862-865.

Sullivan C E, Issa F G (1985). Obstructive sleep apnea. *Clinics in Chest Medicine*; 6: 633-650.

Swinscow T D V (1976). The  $\chi^2$  test. *Br Med J*; 2: 513-514.

Taasan V C, Block A J, Boysen P G, Wynne J W (1981). Alcohol increases sleep apnea and oxygen desaturation in asymptomatic men. *Am J Med*; 71: 240-245.

Tabachnik E, Muller N L, Bryan A C, Levison H (1981a). Changes in ventilation and chest wall mechanics during sleep in normal adolescents. *J Appl Physiol*; 51: 557-564.

Tabachnik E, Muller N L, Levison H, Bryan A C (1981b). Chest wall mechanics and pattern of breathing during sleep in asthmatic adolescents. *Am Rev Resp Dis*; 124: 269-273.

Tai E, Read J (1967). Blood-gas tensions in bronchial asthma. *Lancet*; 1: 644-646.

Tepper R S, Skatrud J B, Dempsey J A (1983). Ventilation and oxygenation changes during sleep in cystic fibrosis. *Chest*; 84: 388-393.

Thorowgood J C (1878) in *Notes on asthma, its nature, forms and treatment*. Churchill, London.

- Timmons B, Salamy J, Kamiya J, Girton D (1972). Abdominothoracic respiratory movements and levels of arousal. *Psycho Sci*; 27: 173-175.
- Tinkelman D G, Moss M A, Bukantz S C, Sheffer A L, Dobken J H, Chodosh S, Cohen B M, Rosenthal R R, Rappaport I, Buckley C E I, Chusid E L, Deutsch A J, Settipane G A, Burns R B P (1985). A multicenter trial of the prophylactic effect of ketotifen, theophylline, and placebo in atopic asthma. *J Allergy Clin Immunol*; 76: 487-497.
- Trask C H, Cree E M (1962). Oximeter studies on patients with chronic obstructive emphysema, awake and during sleep. *N Engl J Med*; 266: 639-642.
- Trousseau A (1868) in *Lectures on clinical medicine* (Translated V Barzine). Volume I. New Sydenham Society, London.
- Turino G M, Goldring R M (1978). Sleeping and breathing. Editorial. *N Engl J Med*; 299: 1009-1010.
- Turner-Warwick M (1977). On observing patterns on airflow obstruction in chronic asthma. *Br J Dis Chest*; 71: 73-86.
- Turner-Warwick M (1984). The definition and recognition of nocturnal asthma. In: Barnes P J, Levy J, eds. *Nocturnal asthma. International Congress and Symposium Series, No 73*, London: The Royal Society of Medicine, 3-9.
- Tusiewicz K, Moldofsky H, Bryan A C, Bryan M H (1977). Mechanics of the rib cage and diaphragm during sleep. *J Appl Physiol*; 43: 600-602.
- Tweeddale P M, Leggett R J E, Flenley D C (1976). Effect of age on oxygen-binding in normal human subjects. *Clin Sci*; 51: 185-188.
- Tweeddale P M, Leggett R J E, Flenley D C (1977). Oxygen affinity in vivo and in vitro in chronic ventilatory failure. *Clin Sci*; 52: 277-281.
- Ulmer W T (1975). Dose-and time-response of Sch 1000 MDI and other inhaled bronchodilators. *Postgrad Med J*; 51 (supplement 7): 138-140.
- Vella L M, Hewitt P B, Jones R M, Adams A P (1984). Sleep apnea following cervical cord surgery. *Anaesthesia*; 39: 108-112.
- Walsh J T, Montplaisir J (1982). Familial glaucoma with sleep apnoea: a new syndrome? *Thorax*; 37: 845-849.
- Webb P (1974). Periodic breathing during sleep. *J Appl Physiol*; 37: 899-903.
- Webb W B, Campbell S S (1979). The first night effect revisited with age as a variable. *Waking sleeping*; 3: 319-324.

Weil J V, Jamieson G, Brown D W, Grover R F (1968). The red cell mass-arterial oxygen relationship in normal man. J Clin Invest; 47: 1627-1639.

Weil J V, Byrne-Quinn E, Sodal I E, Friesen W O, Underhill B, Filley G F, Grover R F (1970). Hypoxic ventilatory drive in normal man. J Clin Invest; 49: 1061-1072.

Weiner N (1980). Norepinephrine, epinephrine and the sympathomimetic amines. In: Goodman A G, Goodman I S, Gilman L A, eds. The pharmacological basis of therapeutics, sixth edition, New York: Macmillan.

Wells A, Taylor B (1979). A placebo-controlled trial of ketotifen (HC 20-511, Sandoz) in allergen induced asthma and comparison with disodium cromoglycate. Clin Allergy; 9: 237-240.

Westerman D E, Benatar S R, Pogieter P D, Ferguson A D (1979). Identification of the high risk asthmatic patient. Experience with 39 patients undergoing mechanical ventilation for status asthmaticus. Am J Med; 66: 565-572.

White D P, Douglas N J, Pickett C K, Weil J V, Zwillich C W (1982). Hypoxic ventilatory response during sleep in normal premenopausal women. Am Rev Resp Dis; 126: 530-533.

White D P, Douglas N J, Pickett C K, Zwillich C W, Weil J V (1983). Sleep deprivation and the control of ventilation. Am Rev Resp Dis; 128: 984-986.

White D P, Miller F, Erickson R W (1983). Sleep apnea and nocturnal hypoventilation after western equine encephalitis. Am Rev Resp Dis; 127: 132-133.

White D P (1985). Central sleep apnoea. Clinics in Chest Medicine; 6: 623-632.

White D P, Weil J V, Zwillich C W (1985). Metabolic rate and breathing during sleep. J Appl Physiol; 59: 384-391.

Wilkinson R T, Stretton M (1971). Performance after awakening at different times of night. Psycho Sci; 23: 283-285.

Williams R L, Karacan I, Hirsch C (1974). EEG of human sleep. New York: Wiley.

Williams S J, Winner S J, Clark T J H (1981). Comparisons of inhaled and intravenous terbutaline in acute severe asthma. Thorax; 36: 629-631.

Willis T (1679). Pharmacutiae rationalis. London: Dring, Harper and Leigh.

Woolcock A J, Read J (1966). Lung volumes in exacerbations of asthma. *Am J Med*; 41: 259-273.

Wuethrich B, Radelovic P, Debelic M (1978). The protective effect of a new oral anti-asthma agent (ketotifen, HC 20-511) against experimentally induced bronchospasm (5 different models). *Int J Clin Pharmacol*; 16: 424-429.

Wynne J W, Block A J, Hemenway J, Hunt L A, Flick M R (1979). Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). *Am J Med*; 66: 573-579.

Zedda S, Sartorelli E (1971). Variability of plethysmographic measurements of airway resistance during the day in normal subjects and in patients with bronchial asthma and chronic bronchitis. *Respiration*; 28: 158-166.

Zimmerman P V, Connellan S J, Middleton H C, Tabona M V, Goldman M D, Pride N B (1983). Postural changes in ribcage and abdominal volume-motion coefficients and their effect on the calibration of a respiratory inductive plethysmograph. *Am Rev Resp Dis*; 127: 209-214.

Zwillich C W, Sutton F D, Neff T A, Cohn W A, Matthay R A, Weinberger M M (1975). Theophylline induced seizures in adults: correlation with serum concentrations. *Intern Med*; 82: 74-75.

Zwillich C W, Natalina M R, Sutton F D, Weil J V (1978). Effects of progesterone on chemosensitivity in normal men. *J Lab Clin Med*; 92: 262-269.

# IRREGULAR BREATHING AND HYPOXAEMIA DURING SLEEP IN CHRONIC STABLE ASTHMA

J. R. CATTERALL  
P. M. A. CALVERLEY  
V. BREZINOVA  
N. J. DOUGLAS  
H. M. BRASH  
C. M. SHAPIRO  
D. C. FLENLEY

*Department of Medicine and Respiratory Medicine,  
Royal Infirmary and City Hospital, Edinburgh*

**Summary** Breathing patterns, ear oxygen saturation ( $\text{SaO}_2$ ), and EEG sleep-stage throughout an undisturbed night's sleep were compared in ten adult stable asthmatics and ten age-matched healthy subjects. The two groups slept equally long (5.0–7.2, mean 6.2 h), but the asthmatics slept less well; they had more periods of wakefulness and drowsiness and irregular breathing than did the healthy subjects. They also had greater and more frequent falls in  $\text{SaO}_2$ . Most hypoxaemic episodes occurred in the rapid-eye-movement phase of sleep and were associated with hypopnoea or apnoea, but no patient had a classical sleep-apnoea syndrome. The severity of nocturnal hypoxaemia was related to the level of  $\text{SaO}_2$  when the subjects were awake, but did not correlate with the fall in forced expiratory volume recorded in eight out of ten asthmatics after sleep.

## Introduction

ALTHOUGH nocturnal wheeze in asthma was clearly described by Dr John Floyer (himself an asthmatic) in 1698,<sup>1</sup> it has only recently been associated with a reduced peak expiratory flow rate (PEFR) in the early hours of the morning (the morning dip).<sup>2–4</sup> The wide prevalence of this symptom becomes apparent when asthmatics are asked how they sleep. Furthermore, although death during an asthmatic attack is rare, some,<sup>5,6</sup> but not all,<sup>7,8</sup> surveys have suggested that such deaths are commoner at night.

Recent interest in disordered breathing during sleep<sup>9,10</sup> has revealed profound transient nocturnal hypoxaemia in

patients with the "blue and bloated" pattern of chronic bronchitis and emphysema.<sup>11,12</sup> If hypoxaemia also occurred in asthmatics with nocturnal wheeze, it could contribute to the disturbed sleep and to the occasional death that occurs in attacks. To see if asthmatics become hypoxaemic during sleep, we examined the relationships between EEG sleep stage, breathing irregularities, and ear oxygen saturation in ten adult patients with chronic stable asthma and compared the results with corresponding observations in ten healthy subjects. Controls were age-matched with subjects, since sleep disordered breathing becomes commoner as age advances,<sup>13,14</sup> even in health.

### Methods

We used non-invasive methods to monitor arterial oxygen saturation ( $\text{SaO}_2$ ) and breathing pattern throughout a night's sleep in ten adult asthmatics (seven males, three females; aged 22–59 years, mean 41.2); the same studies were done in ten healthy age-matched subjects (six males, four females; aged 27–57 years, mean 40.5) who had no history of respiratory disease and a normal chest radiograph, forced expiratory volume in 1 s ( $\text{FEV}_1$ ), lung volumes, and transfer factor for carbon monoxide ( $\text{TCo}$ ).<sup>15</sup> All subjects were within 15% of their desired weight,<sup>16</sup> and all but one (a 56-year-old asthmatic man whose control was a 55-year-old normal woman) were of the same sex as their controls.

All the asthmatics had reversible airways obstruction, with at least one normal  $\text{FEV}_1$  within the past year. In the 2 years before the study the lowest  $\text{FEV}_1$  was 0.5–2.3 litres, and the highest spontaneous  $\text{FEV}_1$  was 1.3–3.5 litres. Seven had positive prick tests to *Dermaphagoides pteronyssinus* and/or grass pollens, and five had a family history of atopy. All were in a stable state with  $\text{PEFR}$  varying by not more than 30% (mean 13%) when measured four times daily for 3 days before and after the study, and none had had an attack of asthma in the previous 6 weeks. Five had a history of nocturnal wheeze, four took oral prednisolone regularly (5 or 10 mg daily), and two inhaled disodium cromoglycate regularly.  $\beta$  sympathomimetics were withheld for 6 h before the study.

Each subject slept in a quiet darkened room on 2 consecutive nights, the first to get the subject accustomed to the equipment. Only data from the second night were analysed. Thermocouples were used to detect air flow at nostrils and mouth, and an induction stethogram at the third intercostal space anteriorly to record anteroposterior chest diameter.<sup>12</sup> The stethograph may not reflect tidal volume in all sleep stages, particularly since Tabachnik et al. have described paradoxical inspiratory indrawing of the rib cage during rapid eye movement sleep (REM) in eight adolescent asthmatics.<sup>17</sup> Ear oxygen saturation was measured by the Hewlett-Packard 47201A ear oximeter.<sup>18</sup> The electroencephalogram (EEG) was recorded for 30 min before "lights out" and throughout the night by two midline frontoparietal electrodes; electrooculogram (EOG) by four electrodes above and outside the outer canthi; and electromyogram (EMG) by two submental electrodes. Sleep stage was analysed by standard criteria.<sup>19</sup>  $\text{FEV}_1$  was measured before the subject went to bed and immediately on waking. The subjects gave informed consent, and the study was approved by the hospitals' ethical committee. Data were recorded on strip chart recorders, EEG, EOG, and EMG being recorded separately and linked by time marks every 15 min to the records of breathing pattern and ear oxygen saturation. Significance of differences was analysed by the Wilcoxon 2-sample test. Values are given as mean and range.

### Results

#### EEG Sleep Stage

The total time spent asleep by all subjects averaged 6.2 h (5.0–7.3) and did not differ significantly between the two groups. There was no significant difference between the two groups in the duration of REM (mean for the two groups 59 min, range 19–84) or of non-REM sleep (NREM; EEG sleep stages 2, 3, and 4) which averaged 227 min (153–290). The

asthmatics spent more time in wakefulness and drowsiness (EEG sleep stages 0 and 1; mean 110 min, 61–160) than did the healthy subjects (mean 64 min, 18–121) ( $p < 0.02$ ).

#### Breathing Pattern

The breathing pattern was fairly regular for most of the time spent asleep, as shown by chest wall movement and oronasal air flow (fig. 1A). Three types of episodes of breathing irregularity were identified—apnoea, "hypopnoea", and "hyperpnoea". Apnoea was defined as complete cessation of oronasal flow for at least 10 s (fig. 1B); hypopnoea as an amplitude of chest wall movement  $\leq 50\%$  of the mean level in the preceding period of regular breathing, lasting for  $\geq 10$  s (fig. 1D); and hyperpnoea as an episode  $\geq 10$  s when the amplitude of chest wall movement was  $\geq 200\%$  of the previous mean level in regular breathing (fig. 1C). Hypopnoea thus defined might arise from paradoxical inspiratory indrawing of the rib cage in REM sleep, as described in adolescent asthmatics.<sup>17</sup> However, our studies of adult stable asthmatics showed that increase in chest diameter at the level of the third intercostal space anteriorly was always in phase with inspiration as recorded by oronasal airflow, even during hypoxaemia in REM sleep.

Over 98% of episodes of breathing irregularity occurred repetitively in short bursts, so that periods of irregular breathing were easily recognised. We timed such periods from the onset of either apnoea, hypopnoea, or hyperpnoea to the start of the next full 2 min of regular breathing. We related these periods to both EEG sleep stage and ear oxygen saturation. We added up the length of each period of irregular breathing to obtain the total duration of irregular breathing for each subject.

Asthmatics spent more time breathing irregularly (mean 52.1 min) than did healthy subjects (mean 24.2 min;  $p < 0.05$ ; fig. 2). In the healthy, hypopnoea accounted for over 99% (70–100) of the irregular breathing, whereas in the asthmatics hypopnoea accounted for 50.4% (0–100) of the irregular breathing, apnoea 40.1% (0–97.7) and hyperpnoea 9.5% (0–24). The 11 apnoeic episodes in the healthy subjects were all of central type. Seven of the asthmatic patients had apnoeic episodes, the number of episodes for each of them being 1, 3, 5, 8, 35, 40, and 71. The frequency of sleep apnoea increased with age, 154/163 (94%) of the apnoeic episodes occurring in the five asthmatics over the age of 40. 151/163 (93%) of the apnoeic episodes in the asthmatics were central, 7 (4%) were obstructive, and 5 (3%) were mixed.

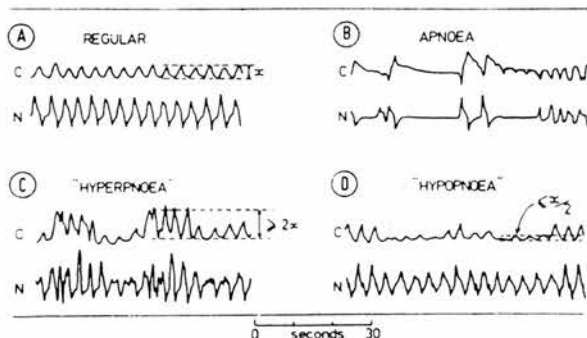


Fig. 1—Classification of breathing patterns.

c = chest wall movement; n = airflow at nostril.

x is the amplitude (in arbitrary units) of the chest wall movement in a subject during stable regular breathing while asleep. In B, an episode of obstructive apnoea (in which chest wall movement continues despite cessation of air flow) is shown following an episode of central apnoea (in which both air flow at chest wall movement cease).



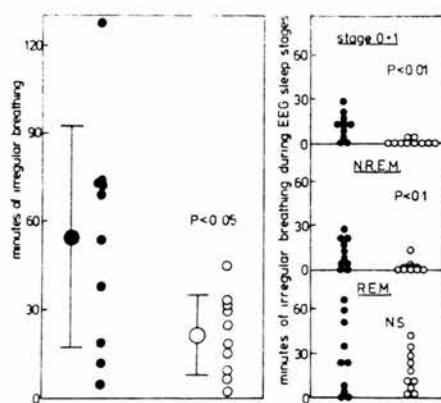


Fig. 2—Duration of irregular breathing (min, mean  $\pm$  1 SD) from sleep onset to final awakening.

Left: total. Right: in wakefulness and drowsiness (EEG sleep stages 0 and 1); in non-rapid eye movement sleep (NREM); and in rapid eye movement sleep (REM) in both asthmatic (●) and healthy (○) subjects.

Although the asthmatics spent more time breathing irregularly than did the healthy subjects in all EEG sleep stages (fig. 2), this difference was significant only during stable wakefulness and drowsiness. Most of the irregular breathing occurred in REM sleep.

#### Arterial Oxygen Saturation

The mean  $\text{SaO}_2$  awake was 95.4% (92.0–97.8 in asthmatics), but 97.0% (95.0–98.5) in healthy subjects ( $p < 0.01$ ). Hypoxaemia during sleep was both commoner and more pronounced in asthmatics, and if a hypoxaemic episode is defined as a fall in  $\text{SaO}_2 \geq 4\%$  from the immediately preceding stable baseline in sleep, such hypoxaemic episodes occurred in nine asthmatics, but in only four of the healthy subjects. These episodes occurred 0–7 times a night in asthmatics, but only 0–1 times a night in the healthy. The lowest  $\text{SaO}_2$  during sleep ranged from 77.0–91.0% (mean 85.0) in the asthmatics, whereas this was 89.3–95.2% (mean 92.8) in the healthy ( $p < 0.01$ ). The mean fall in  $\text{SaO}_2$  from the level awake to the lowest level during sleep was 9.7% (4.0–18.9) in asthmatics and 4.3% (2.0–6.2;  $p < 0.01$ ) in controls (fig. 3).

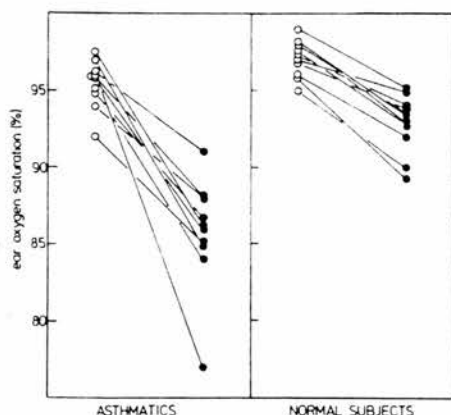


Fig. 3—Pre-sleep (○) and lowest sleep (●) arterial oxygen saturation (%) in asthmatics and controls.

Lines join measurements in individual subjects.

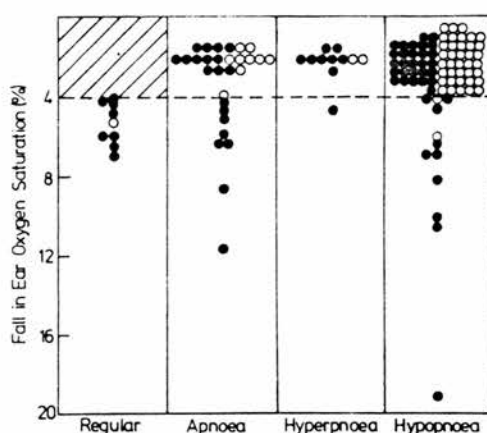


Fig. 4—Relation between breathing patterns and oxygen desaturation in asthmatic (●) and healthy (○) subjects.

Each point represents a period of breathing. The fall in oxygen saturation is from the stable oxygen saturation during sleep.

All 4 hypoxaemic episodes in the controls occurred during uninterrupted REM sleep; 1 was associated with regular breathing, 1 with apnoea, and 2 with hypopnoea (fig. 4). In the asthmatics 16/28 (57%) of these episodes occurred in uninterrupted REM sleep, 3 (11%) in uninterrupted NREM sleep, 6 (22%) in NREM sleep which was interrupted by short periods of wakefulness and drowsiness (EEG sleep stages 0 and 1), and 3 (11%) during stable wakefulness and drowsiness. 8 hypoxaemic episodes in asthmatics were associated with regular breathing, 8 with apnoea, 1 with hyperpnoea, and 10 with hypopnoea (fig. 4). On-line computer recording of chest wall movement and inspiratory and expiratory time for each breath taken throughout the night's sleep showed that in three of the four asthmatics in whom such recording was made expiratory time was longer in hypoxaemic episodes occurring during REM sleep than during periods of NREM sleep when the arterial oxygen saturation was stable (fig. 5). Chest wall movement was also reduced during these hypoxaemic episodes (fig. 5).

In eight asthmatics the  $\text{FEV}_1$  on waking up in the morning was below the  $\text{FEV}_1$  on retiring, the mean value falling from 1.5 litres before sleep to 1.3 litres after sleep. There was no correlation between fall in  $\text{SaO}_2$  during sleep and these changes in  $\text{FEV}_1$ .

#### Discussion

Irregular breathing and episodic hypoxaemia during sleep were both commoner in adult patients with stable asthma than in healthy age-matched controls. The asthmatics also slept less well—they had more intervening drowsiness and wakefulness than the controls. Although Block et al.<sup>14</sup> found that  $\text{SaO}_2$  sometimes dropped in healthy subjects during sleep, this occurred only when the subjects were elderly and obese. None of our subjects (either asthmatic or healthy) was obese. The lowest  $\text{SaO}_2$  values in our asthmatics (91.0–77.0%) were similar to those in eight patients with the "pink and puffing" (type A) chronic bronchitis and emphysema, but much above the lowest  $\text{SaO}_2$  in sixteen "blue and bloated" (type B) bronchitics.<sup>12</sup> Most hypoxaemic episodes were associated with irregular breathing, particularly hypopnoea and apnoea. Apnoea was commoner in asthmatics than in controls. Nearly all apnoeic episodes were central: no patient had a sleep apnoea syndrome.<sup>9,10</sup>

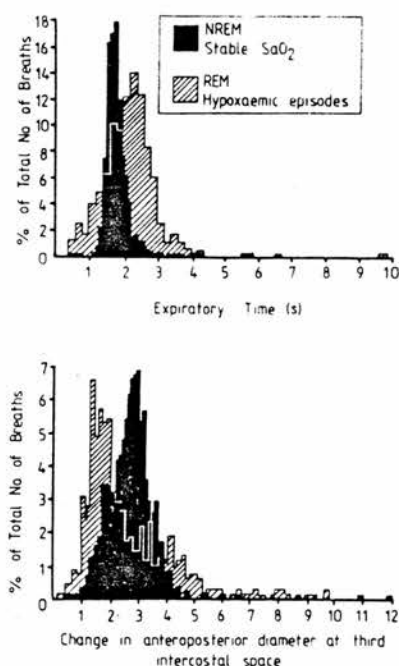


Fig. 5—Lower panel, chest wall movement (antero-posterior diameter at level of third intercostal space anteriorly), in arbitrary units; and upper panel, expiratory time of all breaths during non-REM sleep with stable ear oxygen saturation (■) and during REM sleep with hypoxaemic episodes (▨) in a 51 year old woman with chronic stable asthma.

We cannot prove that hypoxaemia and hypoventilation were associated with bronchoconstriction during sleep. Indeed, paradoxical inspiratory indrawing of the rib cage in REM sleep, associated with increased diaphragmatic but reduced intercostal EMG activity, has been found in adolescent asthmatics.<sup>17</sup> We cannot confirm this, since we only measured mid-thoracic diameter. However, prolongation of expiratory time ( $T_E$ ) in three of four of our adult asthmatics REM who were hypoxic during sleep contrasts with the shortening of  $T_E$  found during REM sleep in adolescent asthma.<sup>17</sup> We believe that this prolongation of  $T_E$ , coupled with a fall in amplitude of chest wall movement, could arise from subclinical bronchoconstriction during REM sleep. The increase in airways resistance would cause the diaphragm, the main inspiratory muscle, to generate a greater inspiratory pressure, if tidal volume were to be maintained; however, the increase in lung volume associated with bronchoconstriction<sup>20,21</sup> would further impair its efficiency as a pressure generator. It is uncertain whether sleep itself causes bronchoconstriction in man,<sup>2,21,22</sup> but our preliminary results suggest some association, since the "morning dip" in PEFR is often associated with REM sleep.<sup>23,24</sup> Clearly, better methods of detecting bronchoconstriction which do not depend upon the patient being awake are needed to resolve this question.

In our chronic stable asthmatics FEV<sub>1</sub> measured before and after sleep was a poor guide to the fall in SaO<sub>2</sub> during sleep. However, this fall in SaO<sub>2</sub> correlated with the awake SaO<sub>2</sub> ( $p < 0.05$ ) when the results for both asthmatics and healthy subjects are combined. Conversion of SaO<sub>2</sub> values into corresponding arterial PO<sub>2</sub> (assuming a normal oxygen dissociation curve and pH) yields a significant correlation ( $n = 20$ ,  $r = 0.66$ ,  $p < 0.01$ ):

$$\begin{aligned} \text{Lowest PaO}_2 \text{ asleep (mm Hg)} \\ = 0.35 \times \text{PaO}_2 \text{ awake (mm Hg)} + 28. \end{aligned}$$

This means that asthmatics have a lower SaO<sub>2</sub> during sleep, partly because they start the night at a lower point on the oxygen dissociation curve. Our studies do not indicate the differences in roles played by alveolar hypoventilation and/or ventilation/perfusion mismatching in producing the hypoxaemia. To do so will require continuous measurement of arterial PCO<sub>2</sub> as well as ear oxygen saturation, but this is not yet possible by non-invasive means, at least in adults.

Our demonstration of irregular breathing and transient but modest hypoxaemia during sleep in adults with chronic stable asthma, which we suggest may arise from subclinical bronchoconstriction during sleep, may imply that such changes could be more pronounced in patients with severe asthma, or in those recovering from an asthmatic attack. If further studies confirm this suggestion, such hypoxaemia may contribute to the rare but tragic deaths from nocturnal asthmatic attacks. Furthermore, these observations suggest that future studies of drug regimens in asthma should include sleep monitoring, since spontaneous nocturnal bronchoconstriction is common and physiologically important.

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Correspondence should be addressed to D. C. F., Department of Respiratory Medicine, City Hospital, Greenbank Drive, Edinburgh EH10 5SB.

#### REFERENCES

- Floyer J. A Treatise of the asthma. London: R. Wilkin and W. Innys. 1698: 7-8.
- Clark TJH, Hetzel MR. Diurnal variation of asthma. *Br J Dis Chest* 1977; 71: 87-92.
- Connolly CK. Diurnal rhythms in airway obstruction. *Br J Dis Chest* 1979; 73: 357-66.
- Barnes P, Fitzgerald G, Brown M, et al. Nocturnal asthma and changes in circulating epinephrine, histamine and cortisol. *N Engl J Med* 1980; 303: 263-67.
- Cochrane GM, Clark TJH. A survey of asthma mortality in patients between ages 35 and 64 in the Greater London hospitals in 1971. *Thorax* 1975; 30: 300-05.
- Hetzel MR, Clark TJH, Branthwaite MA. Asthma: analysis of sudden deaths and ventilatory arrests in hospital. *Br Med J* 1977; i: 808-11.
- Macdonald B, Macdonald ET, Seaton A, Williams DA. Asthma deaths in Cardiff 1963-1974: 53 deaths in hospital. *Br Med J* 1976; i: 721-23.
- Macdonald B, Seaton A, Williams DA. Asthma deaths in Cardiff 1963-1974: 90 deaths outside hospital. *Br Med J* 1976; i: 1493-95.
- Guilleminault C, Tilkian A, Dement WC. The sleep apnoea syndromes. *Annu Rev Med* 1976; 27: 465-84.
- Guilleminault C, van den Hoed J, Mitler MM. Clinical overview of sleep apnoea syndromes. In: Guilleminault C, Dement WC, eds. *Sleep apnoea syndromes*. New York: Alan R. Liss, 1978.
- Flick MR, Block AJ. Continuous in-vivo monitoring of arterial oxygenation in chronic obstructive lung disease. *Ann Intern Med* 1977; 86: 725-30.
- Douglas NJ, Calverley PMA, Leggett RJE, et al. Transient hypoxaemia during sleep in chronic bronchitis and emphysema. *Lancet* 1979; i: 1-4.
- Webb P. Periodic breathing during sleep. *J Appl Physiol* 1974; 37: 899-04.
- Block AJ, Boysen PG, Wynne JW, et al. Sleep apnea, hypopnea and oxygen desaturation in normal subjects, a strong male predominance. *N Engl J Med* 1979; 300: 513-17.
- Cotes JE. Lung function. Oxford: Blackwell, 1979.
- Documenta Geigy. Basle: Geigy Pharmaceuticals, 1970: 712.
- Tabachnik E, Muller NL, Levison H, Bryan CA. Chest wall mechanics and pattern of breathing during sleep in adolescent asthmatics. *Am Rev Res Dis* 1981; 124: 269-73.
- Douglas NJ, Brash HM, Wraith PK et al. Accuracy, sensitivity to carboxyhaemoglobin and speed of response of the Hewlett Packard 42701A ear oximeter. *Am Rev Res Dis* 1979; 119: 311-13.
- Rechtschaffen A, Kales A. Manual of standardised terminology, techniques and scoring system for sleep stage of human subjects. Washington DC, Public Health Service, U.S. Government Printing Office, 1968.
- Woolcock AJ, Read J. The static elastic properties of the lungs in asthma. *Am Rev Res Dis* 1968; 98: 788-94.
- McFadden, Jr, ER, Lyons HA. Serial studies of factors influencing airway dynamics during recovery from acute asthma attacks. *J Appl Physiol* 1969; 27: 452-59.
- Hetzel MR, Clark TJH. Does sleep cause nocturnal asthma? *Thorax* 1979; 34: 749-54.
- Malo JL, Walsh J, Montplaisir J. Sleep analysis of asthmatic subjects affected with nocturnal attacks. *Am Rev Res Dis* 1980; 121 (suppl): 162.
- Shapiro CM, Montgomery I, Catterall JR. Breathing, bronchoconstriction and sleep in nocturnal asthma. *Thorax* (in press).